

**FACTORS AFFECTING DAYTIME FUNCTION IN THE SLEEP
APNOEA/HYPOPNOEA SYNDROME**

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ABSTRACT

The sleep apnoea/hypopnoea syndrome (SAHS) is characterised by repetitive upper airway obstructions during sleep, which lead to recurrent hypoxaemia and brief arousals from sleep. SAHS patients suffer from excessive daytime sleepiness (EDS), cognitive impairments and decreased psychological well-being. Previous studies have examined relationships between the nocturnal events of SAHS and a limited number of daytime function measures, frequently in small, non-consecutive patient samples. Relationships found have been either weak or non-significant. This thesis examines the relationships between a wide range of nocturnal sleep and breathing variables and daytime function. Additionally, this thesis examines the use of subjective and objective measures of daytime sleepiness, to determine which tests provide the most useful information for SAHS patients.

A pilot study found that neither the 103 patients' nor their partners' Epworth rating of sleepiness were strong predictors of SAHS severity. In 150 patients with a wide range of SAHS severity, relationships between nocturnal events and daytime function were examined using newer definitions of arousal and measures of sleep continuity. A broad battery of daytime tests were used including the maintenance of wakefulness test (MWT) and the short form (SF)-36. Unlike previous studies, all correlations were controlled for age and awake oxygen saturation, known to influence the variables measured. The current study also examined these correlations in an unselected patient sample with a range of disease severity. The study found a lack of strong relationships between conventional nocturnal sleep and breathing variables and daytime function. Few baseline variables significantly predicted CPAP use.

Daytime function measures were compared within the 150 patients. The multiple sleep latency test (MSLT) and the MWT displayed a moderate, discordant relationship. Measures of cognitive function, psychological well-being and subjective sleepiness

better related to the MWT than MSLT, suggesting that the MWT may be a more useful tool in assessing functional impairment in sleep apnoea.

A randomised cross-over study, on 12 SAHS patients, compared daytime sleepiness measured following a night's sleep at home (as performed in this thesis) versus a night in the sleep centre (standard protocol). Preliminary results indicated that daytime sleepiness, as measured by the MSLT and MWT, was not significantly different between the two study limbs. This suggests that the non-standard method of conducting the MSLT and MWT in this thesis does not explain the lack of correlational relationships between nocturnal measures and daytime sleepiness.

The studies presented in this thesis demonstrate a lack of identified factors affecting daytime function in a group of unselected SAHS patients. This may be due to inter-individual patient variability. Also, more sophisticated nocturnal SAHS measures should be examined, as should more 'real-life' daytime assessments, such as ambulatory EEG recorded during a patient's normal daily routine.

For Jon

DECLARATION

I declare that I have been the principal investigator in all the studies conducted within this thesis and that the contents of this thesis are my own work. Assistance with these studies was provided by staff members of the Edinburgh sleep centre, and are detailed in the acknowledgements.

The studies comprising this thesis were conducted within the sleep centre of the Royal Infirmary, or as domiciliary sleep studies within Edinburgh, between 1994 - 1998.

Ruth N. Kingshott

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ABBREVIATIONS

AHI	Apnoea + Hypopnoea Index
ASDA	American Sleep Disorders Association
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
ECG	Electrocardiogram
EEG	Electroencephalograph
EMG	Electromyogram
EOG	Electro-oculography
EPQR	Eysenck Personality Scale - Revised
ESS	Epworth Sleepiness Scale
FCRTT	Four Choice Reaction Time Test
FLP	Functional Limitations Profile
FOSQ	Functional Outcomes of Sleep Questionnaire
HAD	Hospital Anxiety and Depression
IQ	Intelligence Quotient
MCS	Mental Components Summary
MMPI	Minnesota Multiphasic Personality Inventory
MRI	Magnetic Resonance Imaging
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NART	National Adult Reading Test
NHP	Nottingham Health Profile
OSLER	Oxford Sleep Resistance (test)
PASAT	Paced Auditory Serial Addition Task
PCS	Physical Components Summary
PIB	Patient Interface Box
PLMD	Periodic Limb Movement Disorder
PSG	Polysomnography

RAR	Respiratory Related Arousal
TDI	Respiratory Disturbance Index
REM	Rapid Eye Movement (sleep)
SAHS	Sleep Apnoea/Hypopnoea Syndrome
SDB	Sleep Disordered Breathing
SF-36	Short Form 36
SOL	Sleep Onset Latency
SSS	Stanford Sleepiness Scale
SSWI	Stage Shifts to Wake Index
SURT	Simple Unprepared Reaction Time
SWS	Slow Wave Sleep
TIB	Time In Bed
TST	Total Sleep Time
UARS	Upper Airway Resistance Syndrome
UPPP	Uvulopalatopharyngoplasty
WAIS-R	Wechsler Adult Intelligence Scale (Revised)

Chapter 1

Clinical Overview of the Sleep Apnoea/Hypopnoea Syndrome

1.1 Introduction

Since its original recognition only 30 years ago (Jung et al 1965, Gastaut et al 1966), the sleep apnoea/hypopnoea syndrome (SAHS), has been well researched. It is estimated to affect between 1-2% of middle-aged women and 2-4% of middle-aged men (Young et al 1993). Sleep apnoea is characterised by recurrent upper airway collapse (Remmers et al 1978) causing arousal from sleep (Phillipson & Sullivan 1978, Sullivan & Issa 1980) and associated sleep fragmentation and hypoxaemia. Daytime consequences include excessive daytime sleepiness (Roth et al 1980), cognitive dysfunction (Greenberg et al 1987) and decreased psychological well-being (Kales et al 1985), the exact causes of which are unclear and are the main focus of this thesis. A detailed review of the sleep apnoea/hypopnoea syndrome follows.

1.2 The Pathophysiology of SAHS

1.2.1 The normal upper airway

The pharynx, unlike the trachea, has no rigid support from cartilage. During wakefulness, inspiration creates a negative intraluminal pressure which tends to occlude the pharyngeal airway. This is opposed by an increase in the activity of the pharyngeal dilator muscles, in particular the genioglossus and palatoglossus muscles. Upper airway patency is maintained by a balance between these two opposing forces of collapse and dilation. When an individual goes to sleep, there is a decrease in muscle tone, including those dilator muscles situated in the upper airway. In normal individuals the airway lumen remains wide enough to compensate for this balance shift, but in SAHS patients, upper airway narrowing outweighs the dilation, resulting in upper airway collapse with clinical consequences.

1.2.2 The upper airway of an SAHS patient

Studies have used techniques such as acoustic reflection and Magnetic Resonance Imaging (MRI) to demonstrate that awake SAHS individuals have narrow upper airways (Bradley et al 1986, Shelton et al 1993), increased pharyngeal resistance (Suratt et al 1985) and increased pharyngeal compliance (Issa & Sullivan 1984, Brown et al 1985, Suratt et al 1985), compared to normals. A number of predisposing risk factors may contribute to these characteristic upper airway features in sleep apnoeics.

- **Obesity**

Epidemiological studies (Young et al 1993, Bearpark et al 1995) have demonstrated that obesity is probably the most important risk factor associated with upper airway narrowing during sleep. Obesity is classified as a Body Mass Index (BMI), (the Quetelet index = $\text{weight}/[\text{height}^2]$) of greater than 30 kg/m^2 (Revicki & Israel 1986). Studies have found greater neck circumferences in sleep apnoeics compared to weight and age-matched non-apnoeic snorers and normals (Katz et al 1990, Hoffstein & Mateika 1992), and that neck circumference rather than general obesity demonstrates the best relationship with SAHS severity (Davies & Stradling 1990, Stradling & Crosby 1991a). Using MRI scanning, Horner et al (1989) found more fat deposited in the collapsible region of the pharynx in obese SAHS patients compared to weight-matched controls. These studies hypothesise that a greater fat deposition in the SAHS upper airway decreases airway size, either by anatomically narrowing the airspace, or by indirectly decreasing muscle function, or a combination of both. However, Grunstein et al (1993) found that central obesity, as measured by waist circumference, was more closely related to SAHS severity than BMI or neck circumference. The authors suggested that abdominal and chest wall fat may reduce lung volume or lessen respiratory muscle activity causing ventilatory impairment by a different means. It is possible that both neck and abdominal fat are causative in the pathogenesis of SAHS, although the balance of evidence suggests that neck fat is the most important of the two.

- **Gender**

Men tend to deposit fat more centrally around the abdomen and the neck than women, and this is one of the possible reasons why men are twice as likely to suffer from SAHS (Young et al 1993). Studies examining the anatomical differences in normal men and women report that men have thicker necks (Martin et al 1997a), larger pharyngeal airways (Brooks & Strohl 1992), and longer soft palates (Guilleminault et al 1988a). Whittle et al (1997a) examined the distribution of fat in normal, non-obese males and females, who were age and BMI matched and found that the total volume of neck fat did not differ between the sexes, but the men had significantly larger anterior fat deposits at the level of the palate. These studies in normals suggest that upper airway sex differences may also be present in SAHS patients. One possible explanation for these differences in men and women is the influence of sex hormones. Block et al (1980) found the prevalence of SAHS to increase after the menopause, suggesting progesterone has a protective role as a respiratory stimulant in premenopausal SAHS women. However, in this study, the possible confounding effect of age was not considered. In a similar study by Leech et al (1988), SAHS severity increased with age in both sexes, and it was concluded that the increase in disease severity was due to age as a risk factor and not sex hormones.

- **Age**

Another interrelated SAHS risk factor is middle-age. White et al (1985) found airway resistance to increase with age in normal men, but not women. Men also tend to deposit more fat around the neck, and frequently do this during middle age. This may explain why middle age tends to be the most frequent time for SAHS to develop.

- **Genetic predisposition**

Mathur and Douglas (1995) noted that with increasing recognition and referral rates, thin SAHS patients exist, with 50% of SAHS patient referrals having a BMI < 30 kg/m². In thin SAHS patients it is possible that some anatomical abnormality is contributing to upper airway collapse, such as retroposition of the mandible or the maxillae (Riley et al 1983) narrowing the airway.

SAHS is frequently clustered into family groups. One explanation (Strohl et al 1978), is that obesity is familial and strong links exist between SAHS and obesity. Mathur and Douglas (1995) removed the confounding effect of obesity, by only studying first degree relatives of SAHS patients with a BMI < 30 kg/m². These relatives had significantly more nocturnal events measured by polysomnography, more symptoms, and smaller upper airways than weight, height, age and sex-matched controls. In addition, cephalometry identified these relatives as having significantly more backset mandibles and maxillae, and longer soft palates with wider uvulae (Mathur and Douglas 1995). A study by Redline et al (1995) found familial aggregation of SAHS symptoms which was not fully explained by BMI and neck circumference alone. In addition, Pillar and Lavie (1995) examined familial links in 105 offspring of 45 SAHS patients and found a higher prevalence of SAHS offspring in their sample (47%) than epidemiological studies would estimate (2-4%). These three studies suggest that genetic factors may be involved in predisposing an individual to SAHS.

- **Anatomical factors**

Anatomical abnormalities can cause airway narrowing. These include tonsillar hypertrophy, large tongue size and upper airway mucosal oedema from continuous snoring. Also nasal obstructions, such as a deviated septum, polyps or a previously broken nose may increase airways resistance. In addition, posture has an effect on upper airway collapsibility, increasing when an individual is supine rather than erect (Cartwright 1984, Yildirim et al 1991).

- **Factors affecting upper airway muscle activity**

SAHS risk factors are also known to act by decreasing the activity of the pharyngeal dilator muscles. Such factors include alcohol and sleep. Alcohol will decrease neuromuscular tone in upper airway dilator muscles and hence increase upper airway collapse (Issa & Sullivan 1984). The onset of sleep also decreases pharyngeal dilator muscle activity and the consequences of this in sleep apnoeics is discussed in Section 1.2.4.

In summary, there are a variety of causative risk factors predisposing an individual to SAHS. Some patients will have multiple risk factors, whereas other patients have no known risk factor. Further understanding of the pathogenesis of SAHS is required to be able to identify all individuals at risk from SAHS.

1.2.3 The site of upper airway collapse

The site of upper airway collapse varies between SAHS individuals. Studies have found the most common sites to be retroglossal and retropalatal (Hudgel 1986, Chaban et al 1988). This variation in airway site is probably caused by the heterogeneous nature of the SAHS population and the variety of causative risk factors involved. A fuller understanding of the structure and pathophysiology of the SAHS upper airway will help explain the sequence of nocturnal events that occur as a result of upper airway collapse.

1.2.4 Sequence of nocturnal events in SAHS

During wakefulness SAHS patients' airways remain patent due to compensatory reflexes causing pharyngeal dilator muscles to overcome any airway limitation. This was described in a study by Mezzanotte et al (1992), where the genioglossal muscle in awake SAHS patients functioned at a higher percentage of maximum (41%) than controls (13%), thus compensating for a smaller airway lumen. With sleep onset there is a decrease in general skeletal muscle tone, which also affects the upper airway musculature (Figure 1.1). In SAHS patients with an already narrowed upper airway size when awake (Section 1.2.2), this sleep-related decrease in tone of upper airway dilator muscles may lead to partial (hypopnoea) or total (apnoea) collapse of the pharynx. Once a respiratory event begins, inadequate ventilation may lead to a fall in arterial oxygen levels (hypoxaemia) and a rise in carbon dioxide levels (hypercapnia). As the respiratory event continues, the changes in blood gas tensions can stimulate chemoreceptors leading to an increase in ventilatory effort. This increase in chest wall movement against an occluded airway causes the intra-airway pressure to become more negative and lung mechanoreceptors to be activated. Eventually the respiratory event is terminated, usually by a transient cortical electroencephalographic (EEG) arousal from sleep (Phillipson & Sullivan 1978). It is not fully understood which of

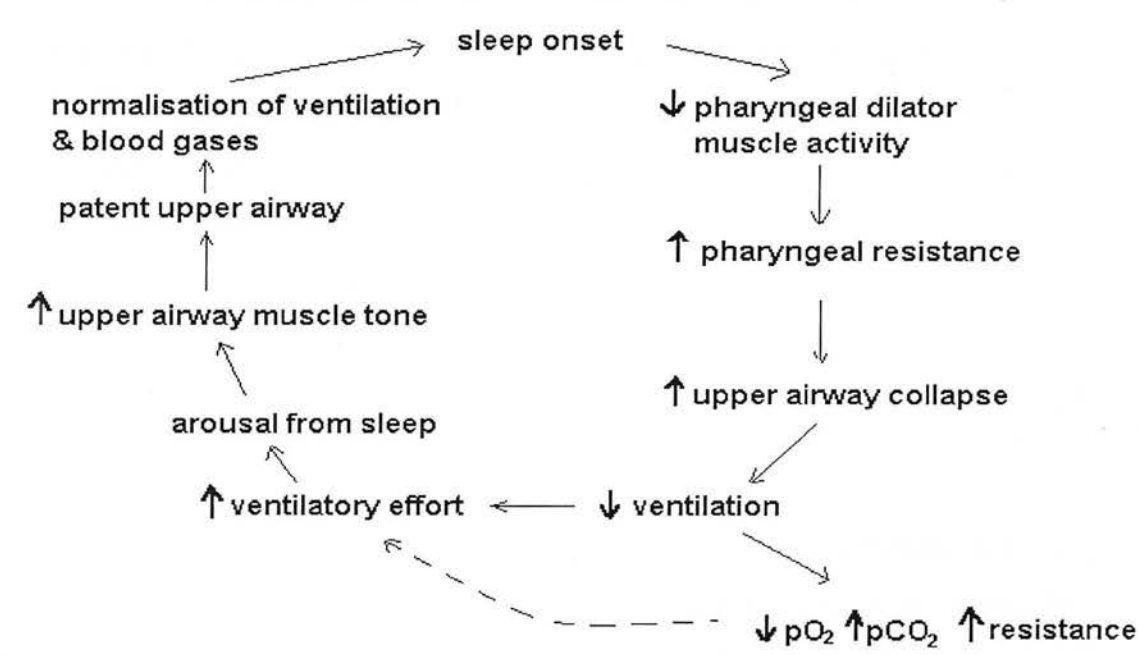
the events during the apnoea leads to its termination. The repetitive changes in blood gas tensions associated with SAHS may cause arousal from sleep and thus apnoea termination. Bowes et al (1981) denervated carotid bodies in sleeping dogs and found that on administering airway occlusion, the arousal response was decreased. The authors suggested that hypoxia activates carotid body chemoreceptors which induce arousal from sleep. Studies have proposed that hypercapnia also causes arousal from sleep. Berthon-Jones and Sullivan (1984) identified this in humans and proposed that hypercapnia acts via nasopharyngeal receptors and medullary chemoreceptors to promote arousal from sleep. More recently, Gleeson et al (1990) hypothesised that the arousal occurs as a result of the increased respiratory effort itself rather than changes in blood gases. In Gleeson's experiments a number of different stimuli were used to increase ventilatory effort (e.g. hypoxic and hypercapnic rebreathing and inspiratory flow resistive loading) in normal subjects. Results showed that each subject would arouse from sleep at the same level of inspiratory effort (oesophageal pressure) for that individual, regardless of the respiratory stimulus. These results were confirmed by Kimoff et al (1994) in SAHS patients. How the increase in respiratory effort promotes arousal is unknown but it is assumed to act via stimulation of the reticular activating system. These authors suggested that mechanoreceptors were important in causing arousal from sleep and that chemoreceptors may play an indirect role by increasing the level of ventilatory effort.

Not all apnoeas and hypopnoeas terminate with a visible EEG arousal from sleep. In some cases only a sub-cortical blood pressure (BP) rise is seen. Davies et al (1993a) used auditory stimuli to arouse healthy normals and found that when an EEG arousal did not occur, they were able to consistently produce BP rises. A study by Rees et al (1995) in SAHS patients also found that not all obstructive apnoeic events terminated in a visible EEG arousal, but did have a postapnoeic BP rise. These blood pressure responses represent subcortical arousals, indicating autonomic activity, and are thought to be clinically significant. Martin et al (1997b), disturbed normal subjects with auditory tones producing subcortical BP arousals. Increases in objective

sleepiness and impaired mood were found in these individuals when compared to an undisturbed night's sleep.

Once a patient has briefly aroused from sleep, there is an increase in upper airway muscle tone, airway patency returns, ventilation and blood gases normalise, the patient then falls back to sleep and the cycle can begin again (Figure 1.1).

Figure 1.1; The Cyclical Nature of Events in the Sleep Apnoea/Hypopnoea Syndrome.



This repetitive cycle of sleeping, decreased ventilation, increased respiratory effort and subsequent arousal seen in sleep apnoea can cause sleep fragmentation and hypoxaemia with associated nocturnal and daytime consequences.

1.3 Clinical Features of SAHS

The sleep apnoea/hypopnoea syndrome is made up of a collection of nocturnal and daytime features. Studies by Guilleminault et al (1978) and Whyte et al (1989) examined SAHS patients from their clinic populations to try and quantify clinical features of SAHS. The main nocturnal feature of sleep apnoea is snoring, reported in 97 - 100% of patients (Guilleminault et al 1978, Whyte et al 1989). This snoring tends to be loud and intermittent. Whyte et al (1989) reported that 35% of bed partners witnessed breathing pauses at night and that nocturnal choking was reported in 26% of SAHS patients. Another common nocturnal feature is restless sleep (36%) (Whyte et al 1989), often caused by motor activity during arousal at apnoea termination. Guilleminault et al (1978) found abnormal motor activity during sleep in all 50 sleep apnoea patients studied, as reported by their bed partners, who most commonly described movements of the arms and legs when struggling to breathe. Other less common nocturnal symptoms reported by patients include nocturia (10%) and occasional enuresis (5%) and a decrease in sexual functioning (6%) (Whyte et al 1989). In the morning after a fragmented night's sleep, many patients (35%) reported feeling unrefreshed on awakening.

Excessive daytime sleepiness (EDS) is the most common daytime symptom associated with SAHS (Guilleminault et al 1976). Whyte et al (1989) defined daytime sleepiness as falling asleep at least once daily whilst not in bed and it was reported in 87% of patients surveyed. Patients also suffer from impaired cognitive function (Greenberg et al 1987, Cheshire et al 1992), often described by patients as a decrease in concentration and poor memory. Personality changes are also frequently reported by family members (48%), and 16% of patients reported clinically significant levels of anxiety or depression (Guilleminault et al 1978). Patients also commonly describe a decrease in quality of life (Guilleminault et al 1976). This can be in terms of marital disharmony, low self esteem or lack of social interactions, for example. These daytime symptoms, their causes and consequences comprise the main theme of this thesis and are discussed further in Chapter 2.

1.4 Definition of the sleep apnoea/hypopnoea syndrome

The term 'Pickwickian Syndrome' was first described by Sir William Osler in 1918, outlining a particular type of patient who resembled 'Joe the fat boy' from Dickens's *Pickwick Papers*, being obese and hypersomnolent. It was then not until 1956 that Burwell et al described additional symptoms associated with this syndrome such as periodic breathing with hypoventilation and associated cor pulmonale. In 1965/66 both Jung and Gastaut's groups independently related these symptoms to breathing pauses during sleep. In 1966, Gastaut described three types of respiratory events in his case report. He described the majority (80%) of events as obstructive apnoeas, defined as a cessation in airflow caused by upper airway obstruction. Central apnoeas were occasionally (15%) seen, where there is no airflow or chest wall movement, possibly due to a disorder of the brainstem. Finally, complex apnoeas (mixed apnoeas) were reported, which start as central apnoeas and then become obstructive in nature, accounting for 5% of cases.

In 1972 the syndrome was named the sleep-induced apnoea syndrome (Sadoul et al 1972). Since this date the diagnostic criteria for clinically significant SAHS has altered over the years. Early definitions included 30 apnoeic episodes, each lasting 10 seconds or more, in both REM (rapid eye movement) sleep and non-REM sleep during a 7 hour period (Guilleminault et al 1976), or more than 5 breathing pauses per hour of sleep (Guilleminault et al 1978), or more than 10 apnoeas per hour of sleep (Lavie 1983). These early definitions were quite arbitrary, but were needed in the first instance for comparisons with future definitions.

It was originally thought that only apnoeas were of clinical relevance. However, Gould et al (1988) identified patients who had no apnoeas, but still had recurrent oxygen desaturations and the clinical symptoms of sleep apnoea. These patients were having hypopnoeas, which are respiratory events caused by upper airway narrowing, but not complete airway occlusion. Gould et al (1988) examined a range of hypopnoea definitions in a group of 50 sleep apnoea patients, to determine the best definition for what was obviously a clinically important arousal causing event. Results

found that a 50% reduction in thoracoabdominal amplitude for >10 seconds, rather than a 50% reduction in airflow, correlated most strongly with the number of arousals from sleep and 4% desaturations (two other measures of SAHS severity). Gould et al's (1988) definition of the sleep apnoea/hypopnoea syndrome (SAHS) required 15 or more hypopnoeas per hour of sleep, (apnoeas defined as the ultimate hypopnoeas), in conjunction with 2 or more major clinical symptoms. This definition is one of many which differ depending on recording techniques and hypopnoea thresholds. Moser et al (1994) performed a survey on 100 accredited US sleep centres and found no consensus in hypopnoea definition. Some labs measure ventilation by airflow and others by thoracoabdominal movement, and the threshold levels of these measures are not well defined. The concurrent inclusion of oxygen desaturations in the criteria also varies.

There is also variation as to what is a clinically relevant level of SAHS disease severity. Lugaresi et al (1983) described a continuum of sleep disordered breathing from mild snoring to severe SAHS. At the mildest end of the range is simple snoring. Lugaresi et al (1978) suggested that snoring was clinically relevant, reporting fluctuations in blood pressure and alveolar hypoventilation associated with the snoring. Hoffstein et al (1995) found an association between snoring and arousal frequency. Both studies suggested that this milder end of the spectrum, snoring, is not just a social nuisance, but has pathophysiological implications. Studies have found decreased daytime alertness in snorers (Guilleminault et al 1991, Stradling et al 1991b), again suggesting clinical consequences of snoring alone. Guilleminault et al (1993) have also focused on this previously neglected mild end of the spectrum. They described a group of individuals who were excessively sleepy in the daytime, but did not have apnoeas, hypopnoeas or sometimes even snoring. By monitoring oesophageal pressure, these individuals were identified as having periods of flow limitation and increased respiratory effort which caused transient EEG arousals from sleep, and hence a possible cause for their daytime sleepiness. This was named the upper airway resistance syndrome (UARS) (Guilleminault et al 1993). Mild forms of SAHS, often classified as <15 apnoeas + hypopnoeas per hour slept (the

apnoea/hypopnoea index - AHI), have also been demonstrated to be clinically significant. Engleman et al (1997a) recently found mild SAHS patients with an AHI between 5 and 15, and 2 or more associated SAHS symptoms, to benefit from continuous positive airway pressure (CPAP) therapy (Section 1.7.3). Mildly affected patients showed improvements in their SAHS symptoms, depression ratings, and cognitive function (Engleman et al 1997a).

Clearly there is still much debate as to what level of sleep-disordered breathing is clinically relevant, and what methods and definition thresholds should be used to quantify these respiratory irregularities .

1.5 Epidemiology

Estimating the prevalence of the sleep apnoea/hypopnoea syndrome in the general population is an extensive task. Firstly, what defines a representative sample of the general population? Secondly, what definition of SAHS should be used?

One of the first epidemiological studies was carried out by Lavie (1983) who surveyed 1,502 Israeli male industrial workers. A screening questionnaire was used to identify a subsample of 300 males, of which 78 agreed to undergo polysomnography. This subsample comprised 17 insomniacs, 20 patients with excessive sleepiness and 41 control subjects. At the time of this early study only apnoeas had been identified, so the diagnostic criteria was chosen as >10 apnoeas /hour slept. Sleep apnoea was estimated to have a prevalence of 0.7% amongst males.

Stradling and Crosby (1991a) studied a more heterogeneous population recruited by age from a general practice. One thousand and one men aged 35-65 years were approached, and 893 agreed to participate. This time, the screening included questionnaires and a physiological measurement, home oximetry. Those with >5 4% oxygen desaturations per hour were asked to attend for in lab polysomnography, and 31/45 agreed. Three of this subgroup were diagnosed as having sleep apnoea.

Therefore a prevalence value for severe, symptomatic sleep apnoea, of 0.3% was estimated.

Jennum and Sjol (1992) studied the prevalence of sleep apnoea in a representative sample of the Danish population aged 30-60 years. Of 1,504 individuals, 748 had limited home monitoring with inductance plethysmography. Sleep apnoea was defined as a respiratory disturbance index (RDI) ≥ 5 with associated hypersomnia, and a prevalence of 0.9% in females and 1.9% in males was found. Young et al's (1993) comprehensive study performed full polysomnography on 602 of 4,284 men and women, participating in the Wisconsin Sleep Cohort Study. All participants were employed and aged 30-60 years old. Prevalence of SAHS was estimated as 2% of middle aged women and 4% of middle aged men. A criteria of an AHI ≥ 5 plus self reported hypersomnolence was used. Most recently, Bearpark et al (1995) studied 294/486 Australian men recruited from a town health volunteer register. All had limited domiciliary recordings measuring snoring, heart rate, oximetry and position. The study found both snoring and sleep apnoea to be of high prevalence within the population. An SAHS prevalence of 3.1% was found, when defined as a respiratory disturbance index (RDI) of >5 oxygen desaturations associated with heart rate changes and snoring sounds. Along with the study by Young et al (1993), these prevalences are higher than previously suggested.

Only 2 studies (Jennum & Sjol 1992, Young et al 1993) examined at the prevalence of SAHS in both men and women, with figures suggesting a ratio of 2 men for every woman having sleep apnoea. Female SAHS patients are therefore underrepresented in sleep clinics, as it is estimated that only one patient in nine seen in the clinic is female (Young et al 1993). Young et al (1996) looked at the differences in referrals between men and women and found that both reported the same major symptoms of snoring and sleepiness, but that women also reported a higher prevalence of atypical symptoms. It was suggested that these additional symptoms may cause misdiagnosis of SAHS in women, being labelled as insomniacs, for example. Also it is thought that some general practitioners may only associate SAHS with obese male Pickwickian stereotypes (Redline et al 1994).

It is difficult to compare the 5 major epidemiological studies described above, which use a variety of techniques and diagnostic thresholds. Davies and Stradling (1996) reanalysed their data on 1,001 Oxford men, in an attempt to make direct comparisons with other studies from abroad, taking into account their definitions and population sample. The prevalence of sleep apnoea in their sample when using $>10\ 4\%$ oxygen desaturations per hour was 1.1%. When the desaturation definition was changed to $>3\%$ per hour, the prevalence rose to 2.7%. Not all individuals with SAHS visibly desaturate with their respiratory events as was shown by Douglas et al (1992), where 34% of SAHS patients remained undiagnosed on oximetry alone. Stradling and Crosby's study (1991a) used oximetry alone and when this was corrected for a 20% 'underreporting factor' in their reanalysis, prevalence rose to 3.6%. Risk factors mentioned in 1.2.2, such as obesity, may differ between population samples. For example, the prevalence rate of obesity in the US and Australia is reported to be 14-16% compared to 8-9% in English men (Bearpark et al 1995). Davies and Stradling (1996) found their SAHS prevalence rose to 4.7% if adjusted for the higher level of obesity in America.

This reanalysis by Davies and Stradling (1996) highlights what effect differences in methodological design, definitions and population sampling can have on the prevalence of a disorder such as the sleep apnoea/hypopnoea syndrome.

1.6 Morbidity and Mortality

Sleep apnoea is a recently recognised disorder, and consequently only limited data are available on its long term consequences. Untreated sleep apnoea is thought to be associated with an increased risk of cardiovascular morbidity including myocardial infarctions, ischaemic heart disease, and cardiac arrhythmia (Ferguson & Fleetham 1995). There is debate as to whether a causative link exists between sleep apnoea and systemic hypertension, with risk factors such as obesity, age, alcohol and antihypertensive therapy, confounding any possible relationship (Levinson & Millman

1991). There may also be an increased risk of cerebrovascular morbidity and mortality related to the cyclical increase in intracranial pressure occurring at the end of an apnoea (Ferguson & Fleetham 1995). Another consequence concerned with increased morbidity and mortality is excessive daytime sleepiness. This symptom may be associated with the 2-7 fold increase in vehicle accidents (George et al 1987, Findley et al 1988) and 3 fold increase in work accidents (Findley 1996) in SAHS patients compared to controls.

Studies have examined survival rates in sleep apnoeics, comparing follow up on different forms of SAHS therapy. He et al (1988) performed a retrospective study on 385/706 male sleep apnoeics. This study found a higher mortality rate in patients with an apnoea index >20 compared to those ≤ 20 . However, this study gave no causes of death. Partinen et al (1988) improved on this by documenting the cause of death. Of 198 patients, 71 underwent tracheostomy (Section 1.7.2), and 127 elected for conservative treatment (weight loss). Survival curves for the two groups were compared and there were 14 deaths in 5 years in the conservative group and none in the tracheostomy group. In addition, the conservatively treated group had a higher cardiovascular mortality rate, suggesting that surgical treatment decreases vascular morbidity. Another retrospective study (Lavie et al 1995) in 1,620 SAHS men and women found a significantly higher mortality rate in the male subgroup aged 30-50 years, with myocardial infarction as the most common cause of death. The study found that age, BMI, hypertension and apnoea index ($AI > 10/\text{hour}$) were all significant predictors of general mortality. Only age and BMI were significant predictors of cardiopulmonary deaths alone. Lavie et al (1995) suggested that SAHS is a risk factor for cardiopulmonary deaths indirectly by acting as a risk factor for hypertension.

The above studies are retrospective and therefore the individuals were not placed randomly into treatment groups. Ideally one needs to carry out a prospective matched controlled study, recruiting patients at an early age, when fewer cardiovascular problems have started and the time since first occurrence of SAHS is less. Patients would then be randomised into treated and untreated groups for long term follow-up. However, this would not be possible, as it is unethical to withhold treatment for an

extended period of time. Recently, a large American cohort study, the Sleep Heart and Health Study, has been set up (Quan et al 1997). This prospective study aims to investigate 6,600 subjects at baseline, for the presence of sleep disordered breathing (SDB) and SAHS, and then monitor at regular follow-up intervals for the incidence of cardiovascular events. The aim being to assess the role of SDB and SAHS as risk factors for cardiovascular disease. Such a large-scale study (Quan et al 1997), which will take into account confounding risk factors, is likely to provide useful answers concerning the long-term morbidity and mortality of SAHS.

1.7 Treatment

Treatments for SAHS can be classified under three main headings: conservative, surgical and non-surgical.

1.7.1 Conservative Treatments

Conservative regimes include weight loss, avoidance of evening alcohol and sleeping in the supine position. Such therapies may help in a few cases (Browman et al 1984), particularly in SAHS patients who cannot tolerate the more obtrusive alternatives. However, benefits from such therapies tend to be short term.

1.7.2 Surgical Treatments

The original surgical treatment for sleep apnoea was to perform a tracheostomy, with the aim of bypassing the obstructed airway (Hill et al 1978). Follow-up studies have shown that this operation normalises sleep disordered breathing (Guilleminault et al 1981) and improves long term survival (Partinen et al 1988). Tracheostomies have been superseded by other treatments requiring less postoperative care, being more acceptable to patients.

The surgical procedure of uvulopalatopharyngoplasty (UPPP) was introduced in 1981 (Fujita et al) to treat snoring. In this procedure the uvula and part of the soft palate are surgically removed. UPPP was also used to treat patients with SAHS, and in the early 80's was a common procedure. UPPP has since fallen out of favour and

the efficacy of this treatment for snoring and SAHS is debatable. It is well known that many simple snorers go on to develop sleep apnoea as they get older, and may therefore require CPAP therapy (Section 1.7.3). By removing pharyngeal and palatal tissues, some individuals cannot tolerate CPAP therapy. This is because a leak can develop between the soft palate and the tongue, and so positive air pressure from the CPAP machine may travel down the nose and then leak out through the mouth, instead of passing down the nasopharynx. Mortimore et al (1996) compared maximum CPAP pressure tolerance in 13 normals, 13 SAHS patients and 13 SAHS patients with a previous UPPP, all matched for age, sex and body mass. Both normals and SAHS patients could tolerate high pressures of 20cm of water, but SAHS patients, with a previous UPPP, tolerated a significantly lower maximum pressure of 14.5 cm of water. This study also found a poorer CPAP run time in UPPP SAHS patients versus SAHS patients matched for age, body mass and AHI. Long-term follow-up has identified poor success rates for UPPP in SAHS patients (Larsson et al 1991) and many snorers (Miljeteig et al 1994). Original UPPP studies may have appeared successful as only subjective improvements in snoring and sleepiness were reported (Miljeteig et al 1994). In addition, He et al (1988) found UPPP treated individuals had a survival rate similar to untreated individuals.

Surgical procedures can be used to successfully remove anatomical upper airway abnormalities such as large tonsils, nasal polyps, or to straighten a deviated septum. Occasionally, reconstructive surgery is performed to advance the mandible and the hyoid bone (Riley et al 1993), in retrognathic SAHS patients. Apart from these procedures, all surgical therapies of SAHS should be considered with utmost caution, as once the soft tissue is removed it is a non-reversible alteration of the upper airway.

1.7.3 Non-surgical Treatments

Various drug treatments have been tried over the years as possible SAHS therapies. Protriptyline, a tricyclic antidepressant, has been found, in some studies to reduce the frequency of apnoeas and hypopnoeas (Clark et al 1979, Conway et al 1982), but not in all studies (Whyte et al 1988). Protriptyline is thought to act by suppressing REM

sleep and therefore removing the longer respiratory events which tend to occur in this sleep stage. Patients have reported troublesome side effects with this tricyclic antidepressant (Whyte et al 1988).

Drug therapies can also be used to treat the daytime consequences of SAHS, such as the daytime sleepiness and poor concentration. Modafinil is a new drug for the treatment of narcolepsy. Modafinil is a novel wake-promoting agent and its exact mechanism of action in the brain is unknown. Arnulf et al (1997) recently performed a randomised placebo controlled, double blind crossover study in sleep apnoeics, with Modafinil. Results found Modafinil to improve objective sleepiness and long-term memory, with no adverse effects on the night-time parameters. Therefore Modafinil may provide part of an adjunct therapy to be used with a nocturnal treatment.

Nasal continuous positive airway pressure (CPAP) (Sullivan et al 1981) is the current treatment of choice for SAHS. This is a mechanical device that consists of a nasal mask connected via tubing to an air pump. CPAP blows a gentle stream of positive pressure air into the patients airway, and mechanically splints the upper airway open. The desired pressure is calibrated by an overnight lab study to find the optimum pressure for each individual considering each sleep stage and posture. Benefits with CPAP can often be seen immediately, but continued use each night at home is required to maintain therapeutic benefit. CPAP has been shown to improve daytime function (Engleman et al 1994a), and long term survival (He et al 1988). In a randomised crossover study, improvements in objective sleepiness, symptoms and cognitive function were found when patients were treated with CPAP rather than an oral placebo (Engleman et al 1994a). A crossover study is currently underway comparing CPAP at optimum pressure and 'sham' CPAP at a suboptimal pressure, in an attempt to confirm the results obtained using a tablet as a placebo. Preliminary data indicates that CPAP improves daytime alertness compared to the 'sham' CPAP (Stradling et al 1998). 'Intelligent' CPAP machines are currently undergoing investigation. These provide a variable CPAP pressure to allow for night to night variability seen in the sleep disordered breathing caused by changes in weight, prior alcohol consumption, sleep stage and posture. Intelligent CPAP should therefore

abolish more respiratory events and hence increase therapeutic effects and therefore compliance. To date, these machines are not routinely available for home use in the UK.

Not all patients will tolerate CPAP as it is an obtrusive device that has to be worn every night. Side effects tend to be minimal though, with nasal stuffiness and pressure sores from masks being the main problems. Patients often comply poorly with CPAP if their initial trial night is not a complete success, or they do not notice subjective improvements in daytime symptoms. Utmost care needs to be taken in educating the patient about CPAP, fitting the correct mask, finding the optimum pressure and providing adequate follow up care. If a patient still does not comply, alternative therapies should be considered.

In the last few years there has been a considerable increase in the number of oral devices on the market (Lowe 1994). These appliances increase upper airway size by repositioning of the mandible (mandibular advancement devices) and/or the tongue (tongue retaining devices). Schmidt-Nowara et al (1995) reviewed 21 publications on oral devices, looking at SAHS patients, pre and post treatment. The summarised data reported that oral devices significantly reduced both snoring and sleep disordered breathing, but not always to normal levels. More recently, a prospective randomised crossover study (Ferguson et al 1996) has been performed. Here SAHS patients used a mandibular device for 4 months and CPAP for 4 months, in a randomised order. Both treatments reduced AHI, with CPAP significantly more so than the oral device. Conversely, side effects and patient satisfaction were greater with the mandibular device. Objective compliance was not measured in this study, and would have been interesting to examine, because with objective compliance taken into consideration, would CPAP still have been the most beneficial therapy? At the current state of play, oral devices may provide a useful alternative to CPAP, especially in sleepy snorers and mild SAHS patients, who may not tolerate CPAP (Schmidt-Nowara et al 1995, Ferguson et al 1996).

In summary, the clinician has to first decide whom requires treatment, and then which treatment to recommend. SAHS severity, symptoms and individual patient requirements all need to be considered. Mechanical therapies such as CPAP and oral devices have the advantage here, because they can be used on a trial basis and then removed if no benefit is derived, and alternatives considered.

Chapter 2

Daytime Function in the Sleep Apnoea/Hypopnoea Syndrome

2.1 Introduction

Patients with SAHS frequently suffer from impaired daytime function (Roth et al 1980, Greenberg et al 1987). The first part of this chapter introduces these daytime impairments, which can loosely be classified into excessive daytime sleepiness, cognitive dysfunction and psychopathology. In addition, the effects of daytime dysfunction on driving performance are discussed. Possible causative effects of repetitive nocturnal sleep fragmentation and hypoxaemia on daytime dysfunction are then described by examining studies on normal subjects and in other disease states, and previous work on SAHS patients (Greenberg et al 1987, Roehrs et al 1989, Cheshire et al 1992, Poceta et al 1992). Treatment related improvements in daytime function are also discussed.

2.2 Excessive Daytime Sleepiness

Excessive daytime sleepiness is the most common daytime feature associated with SAHS, reported in 78-87% of patients surveyed (Guilleminault et al 1978, Whyte et al 1989). In addition to the direct problems caused by daytime sleepiness, SAHS patients have further indirect consequences of sleepiness in the form of an increased risk of vehicle accidents (George et al 1987, Findley et al 1988), decreased subjective work performance (Ulfberg et al 1996), and decreases in cognition and psychological well-being (Greenberg et al 1987, Cheshire et al 1992). These consequences indicate that sleepiness needs to be quantified.

Sleepiness is often poorly recognised by SAHS patients who seem to be unaware of their degree of sleepiness (Dement et al 1978, Engleman et al 1997b), or may not

admit to their sleepiness because of its potential effect on their ability to drive or earn their living. Various tests have been devised to try and quantify daytime sleepiness using both subjective and objective measures.

2.2.1 Subjective daytime sleepiness

The Stanford sleepiness scale (SSS) is a simple 7 point scale from which a patient has to rate their level of sleepiness at a single point in time (Hoddes et al 1973). Early validation studies found SSS scores to correlate with performance measures in normal subjects before, during and after a period of sleep deprivation (Hoddes et al 1973). The success of the SSS in normal subjects is not reproduced in SAHS patients. Dement et al (1978) studied a group of normal subjects and SAHS patients using both the SSS and a physiological measure of sleepiness, the multiple sleep latency test (MSLT). A significant relationship existed between the SSS and the MSLT in normals, but not in the sleep apnoeics. SAHS patients often cannot accurately rate their own level of sleepiness, and have been observed scoring a high level of alertness on the SSS scale whilst literally falling asleep (Roth et al 1980). The role of the SSS nowadays tends to be in the research field measuring mood state changes under different experimental conditions.

The Epworth sleepiness scale (ESS) has become a widely used measure of subjective sleepiness (Johns 1991, 1992, 1993 & 1994). This scale was devised by Johns in 1991 and differs from the SSS in that it asks an individual to rate their general level of sleepiness in 8 everyday situations in the recent past, rather than at that particular moment. Validation studies performed by Johns (1991, 1993, 1994) demonstrated that the ESS could distinguish between patients with excessive sleepiness and controls, and between snorers and SAHS patients. In addition, ESS scores from sleep apnoeic patients have been reported to be significantly correlated with the MSLT and measures of SAHS severity (Johns 1993, 1994). Reliability studies found the ESS to be reproducible in medical students after 5 months, and to be significantly lower in sleep apnoeics on CPAP therapy compared to baseline (Johns 1992), as has also recently been described by Hardinge et al (1995). Based on Johns' work (1991, 1993,

1997), an ESS score of less than 10 is considered normal, with normals averaging a score of 5, and sleep apnoeics averaging a score of 12.

Sleepiness questionnaires provide useful information for including in the initial clinical assessment of a patient, but caution is required as patients are not always reliable assessors of their own sleepiness. Objective measures of sleepiness may quantify daytime sleepiness better.

2.2.2 Objective daytime sleepiness

The limitations of the SSS led to the development of the multiple sleep latency test (MSLT) which measures physiological sleep onset (Dement et al 1978, Carskadon et al 1986, Thorpy 1992). This test was based on the assumption that patients who are physiologically sleepy will fall asleep faster than patients who are not sleepy when instructed to do so, and will therefore measure degrees of sleepiness severity. The MSLT consists of four or five daytime nap opportunities at 2 hour intervals. For each nap an individual lies down on a bed in a quiet, dark room and is instructed to try and sleep. Sleep is recorded polygraphically using electroencephalography (EEG), electro-oculography (EOG) and electromyography (EMG), and is measured in 30 second epochs. A nap is terminated after 20 minutes if no sleep is seen. If the test is to assess a patient for the occurrence of REM sleep, the test is continued for 15 minutes after the first epoch of sleep. In experimental studies measuring sleep tendency, each nap is terminated after 3 consecutive epochs of stage 1 sleep or the first epoch of any other sleep stage (Carskadon et al 1986). The time from lights out to the first 30 second epoch of sleep is the sleep onset latency, which is averaged across the whole day to give a mean sleep onset latency (SOL).

The MSLT is considered the 'Gold Standard' measure of objective sleepiness and is well-validated and used in both clinical and research situations. An early case-control study (Roth et al 1980) compared hypersomnolent sleep apnoeics with age-matched normals using the MSLT. The apnoeic group were significantly sleepier than the normal control group (mean \pm SD MSLT=2.6 \pm 1.7 mins vs. 12.9 \pm 7.9 mins; $p<0.05$).

However, these mean results show overlap exists between the patient and control group's levels of sleepiness. Normal values for the MSLT have been described as an average sleep latency greater than 10 minutes and pathological sleepiness as less than 5 minutes (Carskadon et al 1986, Thorpy 1992). Mean sleep latencies of between 5 and 10 minutes fall into the 'grey zone', in which both SAHS patients and normals have been shown to overlap (Carskadon et al 1986). The small number of severe sleep apnoeics described by Roth et al (1980) fell asleep within the pathological range, whereas the 466 SAHS patients studied by Roehrs et al (1989) fell asleep in 6 minutes on average on the MSLT, which falls into the grey zone. Therefore medical judgement rather than absolute latency values are required for interpretation (Van den Hoed et al 1981, Carskadon et al 1986). Small but significant treatment related improvements in sleepiness have been reported using the MSLT in patients with SAHS (Engleman et al 1994a).

More recently, a variant of the MSLT has been developed (Mitler et al 1982, Poceta et al 1992), known as the maintenance of wakefulness test (MWT). In this instance the patient is seated comfortably upright on the bed or in an armchair, in a dimly lit room, and is instructed to try and stay awake for four or five tests, evenly spaced across the day. Patients are instructed to remain still and not to sing or read or do anything physical to try and remain awake. Original test protocols performed the MWT for 20 minutes (Browman et al 1983). More recently, studies have run the MWT for 40 minutes to minimise ceiling effects (Poceta et al 1992, Sangal et al 1992a). Sleep onset is defined as for the MSLT, as the first occurrence of 3 consecutive epochs of stage 1 sleep or a single epoch of any other sleep stage (Poceta et al 1992). It has been suggested (Mitler et al 1982, Sangal et al 1992a) that the MWT measures a different physiological ability to the MSLT, that is, the ability to stay awake. Therefore, the MWT may be a more appropriate clinical measure for SAHS patients who have problems staying awake in their daily routine. The MWT remains a relatively new test and so normative values and validation work are still scarce. A recent report on 64 normal individuals found a mean \pm SD MWT sleep latency of 35 \pm 8 minutes (Doghramji et al 1997), compared to a latency of 26 \pm 12 minutes in 322

SAHS patients (Poceta et al 1992). Treatment related improvements in MWT sleepiness have also been demonstrated in groups of 24 (Poceta et al 1992) and 26 (Sangal et al 1992b) SAHS patients, respectively.

Both the MSLT and MWT are time consuming and expensive to perform. Arguably though, these objective tests are useful measures of daytime sleepiness, especially when patients find it hard to differentiate between quiet wakefulness and sleep (Browman and Mitler 1988).

Previous studies have examined the relationship between the ESS and the MSLT (Johns 1991 & 1994, Chervin et al 1997) in patients with disorders of excessive somnolence, including SAHS. Moderately significant relationships were found between these two measures of sleepiness, explaining between 14 and 25% of the variance (Johns 1991 & 1994, Chervin et al 1997). It is possible that relationships are not stronger, due to the ESS being a trait assessment, and the MSLT, a state assessment.

In conclusion, subjective and objective measures identify excessive daytime sleepiness in the SAHS population. However, the cause of this sleepiness is not fully understood (Section 2.8).

2.3 Cognitive Function

An early qualitative study by Guilleminault et al (1977) documented that 60% of SAHS patients self-reported poor attention and an inability to concentrate. A quantitative study by Kales et al (1985) measured cognitive dysfunction in 50 SAHS patients using the Bender Gestalt test and the Wechsler adult intelligence scale (WAIS) or the Wechsler memory scale. 76% of patients displayed some evidence of cognitive impairment, identifying decrements in visuospatial skills, memory and visual

perception. However, this study was uncontrolled, with cognitive measures only compared to standardised normative values.

Case-control studies have since been performed (Greenberg et al 1987, Bedard et al 1991a, Naegele et al 1995), but all were on a small number of subjects. Greenberg et al (1987) examined 14 SAHS patients, 10 sleepy controls with other disorders of excessive somnolence and 14 healthy controls, matched for age, years of education and premorbid intelligence. All groups underwent a diverse range of psychological tests, including the WAIS-R, Bender visual-motor test, trail making B, Purdue pegboard and the Wechsler memory scale. Results found the SAHS group to have greater decrements in attention, motor efficiency and graphomotor ability and to perform significantly worse on a rating of global neuropsychological impairment compared to the sleepy controls and non-sleepy controls.

Bedard et al (1991a), compared a group of 10 severe sleep apnoeics to a group of 10 moderate sleep apnoeics and 10 age and sex-matched controls. All subjects underwent the MSLT and a measure of vigilance, the four choice reaction time test (FCRTT), along with a battery of cognitive function tests. The moderate apnoeic patients performed significantly worse than controls on tests of attention, planning and manual dexterity. These decrements were worse in the severe patient group in whom there were additional decrements in IQ and executive functioning. The study suggested that perhaps discontinuity exists in the progression of sleep apnoea, with some cognitive dysfunction developing with moderate sleep apnoea and worsening with disease severity, with additional new cognitive decrements appearing only in severe disease cases. This group did not measure the frequency of microarousals or hypopnoeas. It would have been interesting to determine whether these two nocturnal measures differed between the 2 groups of sleep apnoeics.

In another study (Naegele et al 1995), SAHS patients and controls, matched for age, education and verbal IQ, were administered cognitive tests measuring executive functioning. Of the tests measuring attention decrements, only one of the three

(STROOP-colour test) was significantly worse in the SAHS group than controls. Conversely, all of the short term memory task scores were significantly worse in the patient group. For long term memory tasks, the patient group were significantly worse on the learning part of the tasks and minimally worse on frontal lobe sensitive tasks. In agreement with Bedard et al (1991a), the study concluded that executive functions are impaired in SAHS patients and some decrements are thought to be related to frontal lobe dysfunctions which the authors suggest may be a consequence of hypoxaemia.

Redline et al (1997) performed a case-controlled study comparing mild SAHS patients (RDI of 10-30, n=32) and normals (RDI<5, n=20) controlling for age, IQ and sex. All individuals underwent cognitive testing examining measures of attention, memory, executive functioning and information processing. Patients performed significantly worse compared to the controls on only 2/13 of the cognitive tests. These two tests were a 10 minute continuous performance test measuring attention and the WAIS-R digit backwards test measuring working memory. In agreement with Bedard et al (1991a), the study concluded that small cognitive decrements are observed in mild SAHS patients, and large, often more complex decrements of executive functioning, are found in more severe patients.

Thus sleep apnoeics probably suffer from a diverse range of cognitive decrements in areas of attention, memory and executive functions. Section 2.8 goes on to discuss the possible aetiology of these dysfunctions and the roles played by nocturnal hypoxaemia, sleep fragmentation and daytime sleepiness.

2.4 Psychopathology

2.4.1 Personality and mood states in SAHS

Psychological impairments have been reported in SAHS patients (Cheshire et al 1992). Personality traits and mood states are frequently assessed using the Minnesota

multiphasic personality inventory (MMPI). Studies using the MMPI on SAHS patients have found 28-56% of patients to have elevated depression scores (Guilleminault et al 1977, Beutler et al 1981, Kales et al 1985). In addition, Kales et al (1985) also documented 35% of patients to have elevated hypochondriasis scores and 29% elevated conversion hysteria scores on the MMPI. The Zung self-rating depression scale (SDS) has also been used in SAHS patients, where 45% of patients scored ratings considered symptomatic of depression (Millman et al 1989). Similar results were reported by Cheshire et al (1992) using the hospital anxiety and depression (HAD) scale (Zigmond & Snaith 1983) with 12 of 29 SAHS patients reporting significant levels of anxiety or depression. These studies identify depression ratings in excess of levels found in normal healthy subjects.

Personality traits have also been documented, for example Klonoff et al (1987) described neurotic personalities in 10 SAHS patients, whilst Platon and Sierra (1992) found 23/35 SAHS patients to suffer from emotional and psychosocial distress compared to matched controls.

The above studies identify depression as the most frequently reported mood state in SAHS patients. It is not known if this possible depression is a direct result of SAHS in terms of sleep fragmentation and hypoxaemia, or whether it is a secondary effect as a result of daytime sleepiness, a low quality of life and low self esteem. Klonoff et al (1987) and Cassel (1993) suggested that the high incidence of depression may be caused by 2 additional features other than primary depression, (1) the type of questions asked in the depression scales and (2) the timing of administering the questionnaires. If the depression scale contains sleep specific questions, such as the Zung self-rating questionnaire, which asks about fatigue, task performance and sleep disruption, answers could be positive if an SAHS patient has either depression, or as a direct result of the nocturnal effects of SAHS. However Cassel (1993) found no signs of clinical depression in a sample of SAHS patients given the Freiburger personality inventory, which contains 138 items, of which only 2 items are related to sleep. The timing of administering the questionnaires may also effect the level of depression

scored. Being given a diagnosis of a long term condition such as SAHS is likely to increase depression ratings rather than the depression being specific to sleep apnoea. This is especially the case in early studies where the only available treatment for SAHS would have been a tracheostomy (Klonoff et al 1987). It is interesting to note that Cassel (1993) assessed the patient group prior to their SAHS diagnosis, and found no evidence of clinical depression.

Irritability is another characteristic seen in some sleep apnoeics (Whyte et al 1989) and reported by family members (Guilleminault et al 1978). Irritability, mood changes and excessive sleepiness can lead to marital problems. Marital stress is commonplace, with couples spending less time together due to patient's irritability, sleepiness and sometimes the spouse moving to a separate bedroom to avoid snoring (Cartwright & Knight 1987). In the case series described by Kales et al (1985), 64% of SAHS patients reported marital and family problems.

These problems of daytime sleepiness, cognitive dysfunction and psychopathology also lead to a decrease in the patient's quality of life and sense of well-being, which are probably the most recent symptoms of SAHS to be formally quantified.

2.4.2 Quality of life

Measures of quality of life, in terms of general health and functional status, have become frequently used in outcome research in recent times. The short-form 36 health status questionnaire (SF-36) is a generic measure of quality of life (Ware & Sherbourne 1992). It contains 8 domains of health status such as vitality, physical functioning and pain (Section 3.5.1). Smith and Shneerson (1995) used the SF-36 in a group of 233 snorers and sleep apnoeics to try and identify whether this questionnaire was sensitive to sleep-related problems. Participants were grouped into snorers, mild SAHS and SAHS patients requiring therapy, based on home oximetry. SF-36 values were compared to normative scores, and the SAHS group requiring therapy scored significantly worse on the SF-36, especially in the dimensions of social functioning and vitality. Only the dimension of general health was not significantly different from

the normative values. Neither the simple snorers or the mild SAHS patients differed in SF-36 scores from the normative values. So although the SF-36 does not have a dimension specific to sleep, there seems to be an indirect effect of sleep apnoea on health status (Smith & Shneerson 1995). A similar study was performed in 108 SAHS patients (Jenkinson et al 1997). Three quality of life questionnaires were given to the patients, (1) the SF-36, (2) the functional limitations profile (FLP) and (3) the EuroQol (EQ-5D). FLP measures the effect of illness on daily activities and can be split into 12 dimensions, and the EQ-5D measures the following domains of mobility, self-care, usual activity, pain and anxiety/depression. Questionnaires were given at baseline and compared to population norms. Scores on the SF-36 and the FLP were low compared to population norms at baseline, indicating that SAHS individuals suffer from an impaired quality of life. This was not found using the EuroQol questionnaire. Both Smith & Shneerson (1995) and Jenkinson et al (1997) identified a range of domains which were affected in SAHS patients that are likely to have an effect on many aspects of an individual's life.

Recently a functional outcomes questionnaire has been designed and validated which is specific for disorders of excessive somnolence (DOES) (Weaver et al 1997). This 30 item questionnaire is known as the functional outcomes of sleep questionnaire (FOSQ), and unlike other non-generic sleep questionnaires (ESS, SSS) does not focus on the sleepiness in isolation but measures how the sleepiness affects daily functioning and quality of life. As part of the questionnaire's validation, the FOSQ could reliably distinguish normals from DOES patients (Weaver et al 1997). Factor analysis identified 5 subscales on the questionnaire, namely activity level, vigilance, intimacy and sexual relationships, general productivity and social outcome. The questionnaire therefore appears to identify a range of functional areas affected by daytime sleepiness in SAHS patients. With further studies at baseline and on therapy, this measure of functional outcomes can be utilised further.

Both the generic (SF-36) and non-generic (FOSQ) functional status measures used in SAHS have advantages. Generic questionnaires can allow cross-disease comparisons,

which can be useful, especially when convincing health purchasers of the consequences of a disease and improvements with treatment. Non-generic measures are also advantageous because of their specificity to the disease and usefulness in identifying who needs therapy.

The results discussed here indicate that sleep apnoeics suffer from a wide range of psychological decrements affecting a diverse range of daily functions and activities. Results depend largely on self-assessed questionnaires and therefore should be interpreted with care, as it is possible some individuals may enhance their scores in an attempt to increase their chance of therapy.

2.5 Driving and performance

A severe consequence of daytime dysfunction in sleep apnoeics is an increased risk of vehicle accidents (George et al 1987, Findley et al 1988) and impaired driving performance (Findley et al 1989, Haraldsson et al 1990a, George et al 1996).

2.5.1 Vehicle accident rates

Population studies

Horne & Reyner (1995) performed a general population study by surveying police databases for accident reports and on-the-spot police interviews in England. The study found that between 16 and 23% of the reported accidents were sleep related. In addition, these sleep related accidents were thought to have a higher rate of morbidity and mortality than other vehicle accidents, due to no prior braking and therefore a greater impact speed (Horne & Reyner 1995). This evidence is supported by Parsons (1986) who found that 25% of vehicle accidents were caused by falling asleep at the wheel, and that these accidents accounted for 83% of all fatalities. However, these studies cannot identify the proportion of sleep-related accidents caused by sleep apnoea patients. Most recently, Young et al (1997) performed a large study examining vehicle accident rates in the general population. Polysomnography was

performed in 913 individuals to evaluate sleep disordered breathing (SDB), and 5 year accident rate was obtained from state databases. The study found that men with SDB (AHI>5) were more likely to have one accident every 5 years than subjects with no SDB. Also men and women with an AHI >15 were more likely to have multiple accidents than subjects with no SDB. Such associations were independent of age, miles driven/year, and alcohol. BMI and education were ruled out as confounders. This population based study is not open to the clinic selection bias, and shows rather disturbingly that people at the mild end of the SDB continuum are more likely to have accidents than normals. This mild group are often not treated even if they present with sleepiness.

SAHS patient studies

Studies in sleep apnoeics (George et al 1987, Findley et al 1988) have also examined government databases of accidents in matched case-control studies. George et al (1987) found sleep apnoeics to have over twice the number of reported vehicle accidents compared to controls, although 7 of the 27 patients studied did not undergo polysomnography to define their SAHS. Findley et al (1988) reported a 7 fold increase in accident rate in sleep apnoeics compared to controls, and 2.6 times the rate of accidents seen in all licensed drivers in Virginia.

Accident reports are likely to provide an underestimation of vehicle accidents because minor accidents are often not reported, and in some cases even severe accidents are not reported, possibly due to criminal activities or insurance purposes.

Studies using self-reported data on SAHS accident rates have also been conducted (Haraldsson et al 1990b, Engleman et al 1997b). Haraldsson et al (1990b) performed a questionnaire based study comparing data from self-reported sleep apnoeics and controls. Both groups had similar rates of multiple vehicle accidents, whereas single vehicle accident rates were 7 times higher in SAHS patients. The main problem of using self-reported data is that patients are likely to underreport their accident rates for fear of losing their driving licence. A retrospective study by Engleman et al

(1997b) questioned SAHS patients on CPAP about their driving habits prior to starting therapy. Originally 23% of patients admitted driving impairment due to sleepiness, whereas this value increased to 37% ($p=0.01$) when questioned on CPAP about their pretreatment accident rate. Thus suggesting that retrospective questioning of SAHS patient accident rate may decrease the underreporting of accidents reported at baseline.

2.5.2 Driving performance tests

Driving-related performance can also be monitored using driving simulators and vigilance tasks. Findley et al (1989) compared the performance of sleep apnoeics and control subjects on two different performance tasks. The Doron simulator used road films of highway, city and rural driving, and monitored steering, signalling, braking and accelerating, whilst the computer simulator, Steer Clear, involves the monotonous task of avoiding obstacles on a two lane road using one computer key to change lanes. Patients with sleep apnoea performed significantly worse than controls on both types of simulator. The authors also reported that the sleep apnoeics performed worse on the more monotonous Steer Clear programme, although only 4 sleep apnoeics used both simulators. Haraldsson et al (1990a) compared 15 SAHS patients and 10 age and sex-matched controls using an advanced driving simulator, in the shell of an actual car. The sleep apnoeic group demonstrated a longer brake reaction time, and increased deviations from the lateral road position than the normal subjects. George et al (1996) developed a simulator known as a divided attention driving test (DADT), which measured both tracking ability (keeping within the road boundaries) and visual search (to look for pedestrians, traffic signals etc.). Sleep apnoea patients performed significantly worse than age-matched controls on all measures, with the greatest difference being in tracking error. SAHS patients were also significantly worse than controls under the influence of alcohol, indicating the severity of driving problems in sleep apnoeics. Driving simulators and vigilance tasks are not the same as real driving and so simulator results may not directly link to driving ability. For example, some individuals may find the simulators entertaining and increase their alertness, while

others may manage to upgrade their performance for 30 minutes for the sake of maintaining their driving licence.

2.6 Aetiology of Daytime Dysfunction

There is much debate as to what determines the decrements in daytime function seen in SAHS patients, and this is the main question of this thesis. Correlational studies in sleep apnoeics have suggested that both sleep fragmentation (Guilleminault et al 1988b, Roehrs et al 1989, Poceta et al 1992) and nocturnal hypoxaemia (Bedard et al 1991b) play causative roles in daytime dysfunction. Before this literature is reviewed, the individual contributions of nocturnal SAHS events will be discussed by examining studies using experimental models of sleep fragmentation and hypoxaemia and their effects on daytime function.

2.7 Experimental Models

The sleep apnoea/hypopnoea syndrome consists of a cycle of nocturnal events (Section 1.2.4) including breathing pauses, brief arousals from sleep, oxygen desaturations and sleep stage changes. These nocturnal variables are all interrelated to a certain degree and so identifying possible causative roles of each individual nocturnal variable on daytime function is a complicated task. By experimentally modelling the two most likely causative variables of sleep disruption and hypoxaemia, their contribution to daytime dysfunction can be explored.

2.7.1 Sleep deprivation

Many experimental studies have interfered with sleep quality and quantity in normal subjects in an attempt to identify daytime effects in terms of sleepiness, performance and mood.

One of the first sleep deprivation studies was performed in 1896 by Patrick and Gilbert, where 3 subjects underwent 90 hours of sleep deprivation. EEG was not available, but physiological changes were noted such as a decreased body temperature, brief lapses into sleep along with decreased vigilance and slower reaction times. In 1949, Bjerner used EEG to physiologically monitor sleep patterns during deprivation experiments. The study found that during sleep deprivation there was a decrease in alpha waves along with the emergence of high amplitude slow waves (since termed 'microsleeps' by Harrison & Horne 1996a). Bjerner (1949) found a decrease in daytime performance associated with the occurrence of these 'microsleeps'. Wilkinson (1964) performed sleep deprivation studies and used performance tasks as outcome measures of sleep loss. He designed reaction time and vigilance tasks which were long, and therefore dull and boring, and found that the longer the monotonous task, the worse the performance, following a period of sleep deprivation.

Total sleep deprivation studies have demonstrated that if you deprive someone of sleep, their sleepiness and performance on monotonous tasks will be impaired, although performance levels may be influenced by motivational factors to a point. For example, Horne & Pettitt (1985a) offered normal subjects a cash incentive to maintain a good performance over a 72 hour sleep deprivation period. Subjects managed to maintain a high level of performance for 48 hours, after which it decreased. Total deprivation studies are important fundamental experiments, but what is the minimum amount of sleep required on which individuals can still function normally?

Wilkinson (1969) performed a comprehensive sleep restriction study where subjects spent 6 weeks in the sleep laboratory. Within each group, sleep was restricted to a set level of sleep for two nights. The levels of sleep were 7.5, 5, 3, 2, 1 and 0 hours. All subjects were randomly given each level of sleep restriction over the six week period. During the periods of sleep restriction, subjects performed the Wilkinson auditory vigilance task (WAVT), the Wilkinson addition task and a coding test. Results demonstrated that following one night of sleep restriction, performance remained

unchanged unless sleep was below 3 hours. Following 2 nights of sleep restriction, performance decreased when sleep was below 5 hours. However, Wilkinson did not measure EEG, and so we have to assume that subjects slept well during their various sleep opportunities. Similar studies to Wilkinson (1969) have since been performed (Carskadon & Dement 1981, Dinges et al 1997). Both studies restricted sleep to 5 hours a night for a 7 night period, and included baseline measurements and a recovery period after the sleep restriction. Carskadon & Dement (1981) found MSLT measured sleepiness to increase from the second to the last day of sleep restriction. Dinges et al (1997) found sleep restriction to cause an increase in sleepiness (SSS), fatigue, tension and mood disturbance, and a decrease in attention (as measured by a vigilance task). A subgroup of 8 subjects underwent MSLTs and in this group sleep onset latencies also decreased with sleep restriction. It appears that as the sleep restriction continues, subjects show decreases in performance and increases in sleepiness. It has been suggested that there is a build up of restorative slow wave sleep debt (Wilkinson 1969, Horne 1987) which cumulatively affects daytime function, with continued sleep restriction.

Sleep restriction experiments reduce sleep quantity, but are not simulating the sleep pattern seen in a sleep apnoeic, which consists of regular brief fragmentation of sleep, disrupting sleep continuity and quality.

2.7.2 Sleep disruption

Bonnet and colleagues performed a number of sleep disruption studies in the 1980's. One such study in 1985 aimed to model the disrupting effects of sleep apnoea by causing an awakening after each minute of sleep over two consecutive nights. 11 normal subjects underwent a baseline night, two sleep disruption nights, and two recovery nights. During the sleep disruption nights, each tone-induced arousal was acknowledged by the subjects who either completed a sleepiness scale, or pressed a button on awakening. The sleep disruption caused non-restorative sleep with increases in stage 1 and wake, and significantly less total sleep, especially slow wave sleep (SWS) and REM. After the two nights of sleep disruption there was a significant

decrease in general performance and an increase in subjective sleepiness compared to baseline (Bonnet 1985).

Bonnet (1986) then asked the question of whether this decreased performance was due to a disruption of sleep continuity or lack of restorative slow wave sleep. On one limb regular sleep disruption occurred, and on the other limb sleep disruption also occurred, but in addition slow wave sleep was eliminated. Experimentally induced awakenings were equal in both conditions. The study found no difference in performance, mood or sleepiness between conditions. Therefore results suggest that the decrease in daytime function is due to the frequency of sleep disruption and not the quantity of slow wave sleep.

In 1987, Downey and Bonnet investigated what level of sleep disruption causes daytime dysfunction. There were 4 experimental conditions: (1) total sleep deprivation for 64 hours, (2) awakened every minute, (3) awakened every 10 minutes and (4) 2.5 hours of undisturbed sleep followed by awakenings at 10 minute intervals for the remainder of the disruption night. For each awakening subjects gave a verbal response and then did a simple performance test. Performance declined across both nights and subjects performed best in the 10 minutes disruption condition after the 2.5 hours of uninterrupted sleep and worst after total sleep deprivation. Interestingly, TST, REM and SWS were greater when fragmented every 10 minutes, than in the 2.5 hour uninterrupted condition, yet performance was better when subjects were allowed a period of continuous sleep. In agreement with Bonnet's 1986 experiment, this study concluded that it is the disrupting of sleep continuity and not the type or quantity of sleep that causes a decreased performance. From Bonnet's set of experiments the sleep continuity theory was developed where an individual needs continuous periods of sleep of greater than 10 minutes to restore function during the day.

A similar study was performed by Magee et al (1987), whose three sleep disruption conditions were (1) an undisturbed night, (2) disruption every minute, (3) disruption every 4 minutes. Daytime sleepiness was assessed by the MSLT. Results showed that

disrupting sleep every minute caused a significant increase in sleepiness. There was no difference in sleepiness between the undisturbed condition and the 4 minute condition. These results might suggest that an individual needs continuous periods of sleep of approximately 4 minutes for sleep to be restorative. This is a lower cut off than that described above by Bonnet (1986).

The experimental sleep disruption in the above studies caused full conscious awakenings requiring behavioural responses. These awakenings led to a decrease in total sleep time (TST) compared to undisturbed control nights and therefore any daytime dysfunction caused by this sleep disruption may be attributed to a lower TST. Thus these awakenings do not closely mimic the sleep fragmentation found in SAHS individuals where arousals tend to be brief (<15 seconds) and therefore only disrupt sleep continuity and not TST (Dement et al 1978).

2.7.3 Sleep fragmentation

In 1987 Bonnet studied eleven subjects who underwent 2 nights of sleep fragmentation, with auditory tones administered at 2 minute intervals. There were 3 conditions of response to arousal, and subjects completed all three conditions over a three week period, (1) a brief awakening followed by a subjective response (Bonnet 1985), (2) a 1/4 body turn in response to the tone, and (3) a change in the EEG (sleep stage change, return of alpha rhythm, or an increase in EEG frequency). The EEG condition was the least disruptive to sleep, having the highest TST, but still eliminated stage 4 sleep along with the other two conditions. Compared to baseline, all three conditions of arousal decreased morning vigilance, nap latency and mood. Therefore it was concluded that a change in the EEG is sufficient to cause daytime dysfunction. The EEG condition of arousal was most representative of SAHS patient's arousals, who tend to have very few remembered awakenings, but many brief arousals (Bonnet 1987). However, there is no record of the actual duration of the changes in EEG frequency in this experiment.

Recent studies (Philip et al 1994, Roehrs et al 1994, Martin et al 1996) have more closely modelled the fragmentation pattern seen in sleep apnoeics and have also taken into consideration the fact that individuals tend to adapt to auditory tones as the night progresses.

Philip et al (1994) applied auditory tones for 5 seconds and immediately determined if there was an arousal response based on a 3 second return to alpha rhythm on the EEG. If no arousal was observed then another 10 second tone was given. Again if no arousal response was observed further tones were given for 10 seconds with gradual increases in sound intensity. One minute of sleep was allowed between arousals. The arousal threshold significantly changed from the first to the third part of the night. Wake time was also monitored to make sure TST was extended on the fragmented night, to match the baseline nights. In the daytime subjects underwent the MSLT and performance tests. Sleep fragmentation caused a significant increase in stage 1 sleep and a decrease in SWS and REM sleep. Fragmentation also increased daytime sleepiness but there was no change in performance measures. A major criticism of the study is that the authors only reported the number of auditory stimulations given, and not the number or maximum length of the resulting EEG arousals, as it is likely that not all stimulations produce the desired arousal.

In a study by Roehrs et al (1994) 36 subjects underwent two consecutive nights of sleep fragmentation, with the MSLT and performance tests carried out on both days. Fragmentation results were compared to an undisturbed night and test day prior to the fragmentation limb, with no difference in TST between both limbs. The auditory tones were created by a computerised tone generator which varied the frequency and intertone interval to decrease adaptation. Tones were given, on average, every 2 minutes on both fragmentation nights. There was no difference in TST between the two fragmentation nights. Results found one night of sleep fragmentation caused an increase in sleepiness as measured by the MSLT, but this did not change any further after the second night of fragmentation. Sleep fragmentation caused no change in performance as measured by a divided attention task. These differences in daytime

sleepiness and lack of performance differences, between unfragmented and fragmented nights have to be interpreted with caution because the unfragmented limb always occurred prior to the fragmented limb and results may be explained by a possible order effect.

To overcome any possible order effect, Martin et al (1996) performed a study on 16 normal subjects using a randomised crossover design. On one limb subjects slept normally, and on the other limb they were fragmented by auditory tones at 2 minute intervals. Both study nights were preceded with an acclimatisation night. Tones were manually administered causing brief arousals from sleep (between 3 and 15 seconds long). Each arousal was preceded by an intertone interval of 2 minutes of stage 2 sleep. If an auditory tone did not produce a visible EEG arousal, a 10 second interval occurred, before a louder or longer tone was given. Both study nights were followed by extensive daytime tests measuring subjective and objective sleepiness, mood and cognitive function. There was no difference in total sleep time between the two study nights, but the fragmented sleep significantly reduced slow wave sleep and REM sleep, and more than doubled the number of microarousals compared to the non-fragmented night. Both objective sleepiness latency, on the MSLT and MWT, and mood were lowered with sleep fragmentation. In addition, performance on trail making B and PASAT (4 secs) were significantly impaired as a result of sleep fragmentation, suggesting decreases in mental flexibility and sustained concentration. This is in contrast to previous studies (Philip et al 1994, Roehrs et al 1994) where no changes in cognitive performance scores were found. This study improves on previous sleep modelling studies by including a control limb, acclimatisation nights on both limbs, and a randomised crossover design.

In summary, sleep fragmentation studies have demonstrated that repetitive brief arousals of a similar duration to those found in SAHS (Martin et al 1997c) cause increased sleepiness (Bonnett 1987, Philip et al 1994, Roehrs et al 1994, Martin et al 1996), and impaired mood and cognitive dysfunction (Martin et al 1996). This leads

to the speculation that sleep fragmentation may play a causative role in SAHS daytime dysfunction.

2.7.4 Modelling hypoxaemia

The repetitive breathing pauses of SAHS lead to falls in arterial oxygen levels. As with experiments modelling sleep loss, modelling hypoxaemia may shed some light onto the possible causative relationships in SAHS patients between hypoxaemia and daytime function (Greenberg et al 1987, Bedard et al 1991b, Cheshire et al 1992).

Studies on the cerebral effects of acute hypoxaemia have been performed on normal subjects at high altitudes. Cognitive dysfunction has been identified at 4,000-6,200m compared to baseline altitudes in measures of constructional ability, problem solving (Nelson 1982a), complex abstract reasoning and verbal fluency (Peteit et al 1988). In addition, psychological changes have been identified including increased paranoia, obsessive-compulsive behaviour, hostility (Nelson 1982a) and psychosocial dysfunctioning (Peteit et al 1988). However, unlike the acute hypoxaemia seen at high altitude, SAHS patients may have suffered long-term hypoxic effects and therefore perform differently on cognitive tasks. Furthermore, SAHS patients tend to have intermittent nocturnal hypoxaemia, not 24 hour hypoxaemia. In addition other factors may contribute to changes in psychological state at altitude, such as feelings of isolation.

An alternative approach is to study the sustained hypoxia seen in patients with chronic obstructive pulmonary disease (COPD), although again, this tends to result in 24 hour hypoxaemia. Case control studies have identified decrements in cognitive function and psychological well-being in hypoxic COPD patients (Grant et al 1982, McSweeney et al 1982, Prigatano et al 1983). One such study (Grant et al 1982) consisted of 203 hypoxic COPD patients involved in the nocturnal oxygen therapy trial (NOTT), along with 74 age, sex and education-matched healthy controls who underwent a cognitive battery measuring motor ability, attention, perceptual-motor performance, sensory function, verbal skills and memory. 42% of COPD patients demonstrated moderate to

severe cerebral impairments compared to only 14% of controls. The higher cognitive functions of abstract thinking and complex perceptual motor integration were most affected, and the authors suggest this could be due to the decreased availability of oxygen to the brain. Prigatano et al (1983) measured a similar diverse range of cognitive functions on a group of 100 mildly hypoxaemic COPD patients and 25 healthy controls. Mild neuropsychological decrements in abstract reasoning, memory and mental flexibility were seen in the COPD group compared to controls. The level of cognitive deterioration was less than that described by Grant et al's (1982) more severely hypoxic group. Patients involved in the NOTT study were also compared to controls using quality of life measures (McSweeney et al 1982), with COPD patients demonstrating decrements in ratings of social functioning, and increases in ratings of depression, anxiety and fatigue. These studies have identified that individuals with COPD frequently suffer from decrements in cognitive function and quality of life. However, as with altitude studies, direct comparisons with sleep apnoea cannot be made. Not only is the pattern of hypoxaemia different, but also COPD patients have poor quality sleep with frequent awakenings (Calverley et al 1982, Fleetham et al 1982).

More recently Roehrs et al (1995) compared cognitive function and sleepiness in SAHS and COPD patients. The SAHS group were sleepier, as measured by the MSLT. Both groups of patients were cognitively impaired when compared to normative scores. The measures of complex and abstract reasoning and motor skills were sensitive to hypoxic deficits, whereas tests measuring attention, tracking, memory and learning were sensitive to sleepiness. The SAHS group performed significantly worse on an attention type task, whereas the COPD group performed significantly worse on a psychomotor task, with the two groups not differing in their tests for memory or complex reasoning. The study therefore suggested that some cognitive deficits are disease specific but others are non-specific. This study again supports the evidence that COPD does not provide an ideal model of SAHS, as the different disease states produce different cerebral impairments. The two groups were not age-matched and age negatively effects cognitive performance (Lezak 1983).

The only study to date which has modelled the intermittent hypoxaemia seen in SAHS patients without either the short term effects of acute hypoxia or the daytime effects of COPD, has induced nocturnal hypoxia in a group of sleep apnoea patients. Colt et al (1991) performed a randomised crossover study on 7 SAHS patients. On one limb of the study, patients were administered CPAP to abolish apnoeas, sleep fragmentation and hypoxaemia for two nights. On the other limb patients were given CPAP to abolish apnoeas and sleep fragmentation for two nights, but this time were also given intermittent additions of 100% nitrogen gas to air to induce repetitive desaturations. Both experimental limbs and two baseline nights were followed by the MSLT to measure sleepiness. Results demonstrated that sleepiness decreased on CPAP compared to baseline, but did not differ between the two CPAP conditions. Therefore the study suggested that hypoxaemia had no independent effect on daytime sleepiness in the absence of sleep fragmentation. The hypoxaemic limb naturally had significantly more desaturations, but there was no difference in arousal frequency between the two study conditions. This study used only a small sample size and a Type II error is thus not excluded.

2.7.5 Conclusion

Modelling studies provide some useful information about the independent roles of sleep fragmentation and hypoxaemia on daytime function. The sleep modelling experiments demonstrated that sleep fragmentation leads to deficits in sleepiness, mood and cognitive function (Martin et al 1996), and that sustained hypoxaemia may lead to wide spread decrements in cognitive function and quality of life, and altered mood states (Grant et al 1982, McSweeney et al 1982).

2.8 Relationships between nocturnal SAHS measures and daytime dysfunction.

The next stage of this chapter is to focus on the possible relationships between nocturnal sleep and breathing events and daytime function, examining relationships within individuals from the whole continuum of sleep disordered breathing. These possible causative relationships comprise the main focus of this thesis.

To clearly present the evidence, the daytime function measures have been subdivided into daytime sleepiness (section 2.8.1), cognitive function (2.8.2) and psychopathology (2.8.3). Obviously there is considerable overlap between these daytime measures, but there are also considerable interrelationships between the nocturnal variables and I felt this was the clearest way to present these results.

2.8.1 Relationships with daytime sleepiness

Many previous research studies have focused on identifying relationships between the nocturnal disturbances associated with sleep apnoea and daytime sleepiness, in an attempt to find a cause of excessive daytime sleepiness (Table 2.1).

Table 2.1; Major correlational studies of daytime sleepiness in SAHS patients

Author	Subjects	Daytime measures	Study Findings
Roth et al 1980	10 severe SAHS 10 controls	MSLT	In sleep apnoeics, RAR related to stage 2 sleep on MSLT, no relationships with stage 1 sleep on MSLT
Stepanski et al 1984	15 SAHS 40 other (15 myoclonus, 15 insomniacs, 10 controls)	MSLT	In SAHS group, only a trend between arousals and MSLT
Guilleminault et al 1988b	100 SAHS	MSLT	Sleep variables (SWS & st 1 sleep) related to MSLT
Roehrs et al 1989	466 SAHS	MSLT	RAR best predictor of MSLT
Bedard et al 1991b	20 moderate-severe SAHS	MSLT FCRTT	Measures of hypoxaemia best predictors of MSLT
Poceta et al 1992	322 SAHS	MWT	RAR best predictor of MSLT
Cheshire et al 1992	29 SAHS	MSLT (+ cognitive function tests & mood scale)	No relationships between nocturnal parameters and MSLT (only with cognitive function)

MSLT=Multiple sleep latency test; RAR=Respiratory related arousals; SWS=Slow wave sleep;

FCRTT=Four choice reaction time test.

Subjective sleepiness

An early study (Orr et al 1979) compared 4 sleepy and 4 asymptomatic patients as defined by the Stanford sleepiness scale and self/family reports. The symptomatic group had lower arterial oxygen tension on waking and during sleep, but no differences in apnoea index or sleep disruption. The study therefore suggested that daytime sleepiness is not influenced by apnoea severity or sleep variables but maybe by hypoxaemia, although the study was very small and results should be interpreted with caution. Johns (1993) examined relationships between nocturnal SAHS measures and subjective sleepiness as part of the validation of the Epworth sleepiness scale

(ESS) and found sleepiness to relate to AHI and hypoxaemia, but recorded no measure of microarousal frequency. These two studies show relationships with sleepiness when measured subjectively. However, subjective sleepiness is not always compatible with measures of objective sleepiness (Dement et al 1978).

Objective sleepiness

The following set of studies all measured daytime sleepiness using objective techniques recording physiological sleep onset. Roth et al (1980) studied 10 severe sleep apnoeics (mean AI = 58) and 10 age-matched controls. All participants underwent full polysomnography followed by sleep latency naps the following day. Correlational analysis found a significant relationship between sleep disruption (shifts to stage 1 sleep, $r=-0.57$; and % stage 1 sleep, $r=-0.52$, no p values reported in text) and daytime sleepiness. When the two groups were analysed independently, the controls showed relationships between shifts to stage 1 sleep and % stage 1 and daytime sleepiness. Whereas in the sleep apnoeic group, no nocturnal sleep or breathing parameter correlated with stage 1 sleep on the daytime naps, only respiratory related arousals correlated with stage 2 latency on the daytime naps ($r=-0.67$). The authors provided two possible explanations for their lack of findings in SAHS patients. Firstly, the current nocturnal measures are not sensitive enough to detect the nocturnal cause of daytime sleepiness. This may be the case, because since this early paper, hypopnoeas and EEG microarousals have been described. Secondly, there may be a lack of variability in the sleepiness of the patient group which is hard to differentiate using the daytime nap latency. In addition, the data was only acquired in 10 severe sleep apnoeics and these numbers are far too small to rely on correlations.

Stepanski et al (1984) focused on the contribution of sleep fragmentation on daytime sleepiness by measuring a range of arousal definitions. Sleep fragmentation was examined in 55 subjects (15 sleep apnoeics, 15 patients with myoclonus, 15 insomniacs and 10 normal subjects) using increasing levels of arousal: (1) increased EEG and chin EMG frequency, (2) alpha burst in EEG of 0-29 secs, (3) sleep stage

shift to a lower stage, (4) a 30 second awakening. Arousal frequencies were correlated with a sleepiness index as measured by the MSLT. All four groups of subjects had significantly different numbers of arousals across all 4 levels. The sleep apnoeic group had more level 1-3 arousals and the least level 4 (awakenings) arousals. The authors suggested this is due to the sleep apnoeic group being the most sleepy and therefore less likely to have full awakenings, possibly due to a higher arousal response from years of adapting to their disease, or simply that they are too sleepy to wake up for more than 29 seconds. In the total sample of 55 subjects, significant correlations existed between total arousal frequency and sleepiness ($r=0.48$, $p<0.001$), but this was not reproduced in the individual groups. In the sleep apnoeics, there was no significant relationship between total arousals and sleepiness on the MSLT. Like Roth et al (1980), these authors suggest that there may not be enough variability in sleepiness within each subject group, masking any possible correlations that are seen in the more diverse whole population. The sample size studied here is too small to rely on correlational analysis. Despite this, Stepanski et al's (1984) paper provides useful information about the importance of the brief microarousals and their effect on sleep continuity in sleep apnoea.

Bedard et al (1991b) and Cheshire et al (1992) also examined nocturnal predictors of daytime sleepiness as measured by the MSLT in small samples of sleep apnoeics. Bedard et al (1991b) measured both sleepiness and alertness (reaction time test) in 20 patients with moderate to severe sleep apnoea. Sleepiness correlated with minimum oxygen saturation ($r=0.54$, $p<0.05$) and % sleep time under 90% oxygen saturation levels ($r=-0.46$, $p<0.05$). Sleepiness did not significantly correlate with sleep disruption or the apnoea index. The microarousal frequency was not measured, so its contribution is not known. Relationships may have been seen with hypoxaemia rather than any other nocturnal measure because the selected population had a minimum desaturation $\leq 80\%$. Conversely, Cheshire et al (1992) found no such relationships between nocturnal SAHS measures and objective sleepiness. This group studied 29 symptomatic SAHS patients (median AHI = 46) who underwent full polysomnography, a battery of cognitive tests and the MSLT. In addition to measures

of apnoeas, hypoxaemia and sleep disruption, Cheshire et al (1992) also measured the frequencies of microarousals and hypopnoeas, yet still none of the nocturnal variables correlated significantly with objective daytime sleepiness. This lack of relationships may be due to the small sample size. Both Bedard et al (1991b) and Cheshire et al (1992) also looked at cognitive function measures and these are discussed in section 2.8.2.

Correlational studies with larger numbers and therefore greater statistical power have also been performed (Guilleminault et al 1988b, Roehrs et al 1989, Poceta et al 1992, Chervin & Aldrich 1998). Guilleminault et al (1988b) studied 100 unselected patients presenting with symptoms of sleep apnoea (mean RDI = 50) using full polysomnography and the MSLT. Only sleep architecture (amount of stage 3 & 4, and stage 1) significantly correlated with sleep latency on the MSLT. There were no significant correlations with respiratory disturbances, hypoxaemia or R & K awakenings (more than 15 seconds of wakefulness). Various post hoc analyses were performed on this SAHS population. Patients were divided into non-sleepy, mildly sleepy and severely sleepy as determined by the MSLT and using analysis of variance no significant differences in sleep variables were seen between the three subgroups. When this population was split into two groups determined by MSLT (>8 mins and ≤8mins), the groups differed in RDI ($p=0.001$), stage 1 sleep ($p<0.001$), SWS ($p=0.002$), REM sleep ($p=0.04$) and awakenings ($p=0.003$) but not for measures of hypoxaemia (all $p>0.42$). Cluster analysis was also performed and could define two groups of SAHS patients as 'sleepy' and 'alert' as measured by the MSLT. This study has shown that only sleep structure could predict sleepiness, and that breathing pauses, hypoxaemia and awakenings failed to correlate. This represented a finding similar to that of Roth et al (1980). The cluster analysis could differentiate sleepy and non-sleepy patients, but interestingly, the sleeper group had a lower respiratory disturbance index than the non-sleepy group. This study did not measure microarousal frequency, only >15 second awakenings and % stage 1, which provide only limited evidence of SAHS sleep fragmentation.

In a recent retrospective study (Chervin & Aldrich 1998), the relationship between AHI and the MSLT was studied. Relationships with the AHI and not microarousal frequencies were examined because this is the variable most often used to clinically define sleep apnoea severity. In 1,146 patients with SDB (mean AHI=31), linear regression analysis found that AHI explained less than 12% of the variance in MSLT measured sleepiness.

Roehrs et al (1989) did incorporate the role of sleep fragmentation to some extent when they performed a large correlational study on 466 sleep apnoeics (mean AI =42), using both polysomnography and the MSLT. Sleepiness significantly correlated with arousals, stage 1 sleep and measures of hypoxaemia. These nocturnal variables themselves were highly interrelated, and using multiple regression, the best single predictor of daytime sleepiness was found to be respiratory related arousals. The measures of hypoxaemia provided 'little or no independent predictive information' (Roehrs et al 1989). The authors therefore concluded that sleep fragmentation causes daytime sleepiness in sleep apnoeics. The population sample used in this study is not well defined and no entry or exclusion criteria were given. The arousal definition used in the study (3 sec or greater increase in EEG or submental EMG or both at termination of respiratory event) does not require a change in EEG to score an arousal. This study provides some evidence of the relationship between sleep fragmentation and daytime sleepiness accounting for 13% of the overall variance in MSLT. Poceta et al (1992) performed a similar study in 322 SAHS patients who had an RDI>5. The mean RDI of the group was 39. All patients underwent polysomnography and the MWT the next day. Pearson correlations found that the arousal frequency, RDI and minimum saturation all significantly correlated with mean MSLT (all $r>0.28$, $p<0.05$). Stepwise regression analysis identified the respiratory related arousals as the most important correlate of the MWT, explaining 12% of the variance, a similar value to that found by Roehrs et al (1989) using the MSLT. The studies by Roehrs et al (1989) and Poceta et al (1992) have found the strongest relationships between nocturnal SAHS measures and daytime sleepiness, predominantly with measures of sleep fragmentation. However, as previously

mentioned, such relationships explain less than 13% of the variance in objective sleepiness, which are only relationships of a moderate strength. There are a few possible explanations as to why these two studies found relationships and others did not. The most obvious of these are the larger sample sizes used, and the use of microarousal definitions.

Research has also focused on the mild end of the disease spectrum, studying individuals with upper airway resistance and snoring. Epidemiological studies (Stradling et al 1991b, Jennum et al 1994) in general community populations have found that self reported snoring relates to subjective daytime sleepiness, independent of SAHS confounders (Stradling et al 1991b). Although these studies contain only subjective reports of snoring and sleepiness, they are large number studies.

A small number of physiological studies (Guilleminault et al 1991, 1993) have also been performed. Guilleminault et al (1991) studied 15 male heavy snorers with an RDI<5 and normal oximetry, and found the RDI and the arousal frequency (EEG arousals of 2-10 seconds) both correlated with sleepiness as measured by the MSLT. In a further experiment (Guilleminault et al 1993), 15 patients diagnosed with idiopathic hypersomnia were found to be objectively sleepy with a mean MSLT of 5.1 minutes and had an elevated arousal frequency of 31 per hour slept. These individuals demonstrated an increase in inspiratory effort prior to a decrease in flow, causing microarousals from sleep. The authors concluded that the daytime sleepiness was not idiopathic, but likely to be caused by the increased upper airway resistance leading to sleep fragmentation in the form of brief microarousals.

The above group of studies provide evidence of the contribution of sleep fragmentation to excessive daytime sleepiness in patients with mild respiratory irregularities. This group of individuals very rarely desaturate at night, therefore the contribution of hypoxaemia is unlikely to be relevant in this sub-population.

In summary, this section has demonstrated that it is likely that causative relationships exist between sleep fragmentation and daytime sleepiness, but that the relationships, at best, are only moderate in strength, and in some cases appear weak or non significant. Thus this area remains controversial and requires further investigation.

2.8.2 Relationships with cognitive dysfunction

Both Greenberg et al (1987) and Bedard et al (1991b) found relationships between hypoxia and measures of cognitive function in 14 and 20 SAHS patients, respectively. Greenberg et al (1987) found significant relationships in only 4 out of a possible 72 correlations, and stated that it is difficult to establish robust relationships between hypoxia and cognitive function. In Bedard et al's (1991b) severe SAHS patients, respiratory and sleep variables (apnoea frequency, awakenings, % wake and hypoxia) together explained 66% of the variance in psychomotor performance. Neither Greenberg et al (1987) or Bedard et al (1991b) used measures of sleep fragmentation in their studies, nor controlled for age in their correlations.

Yesavage et al (1985) only studied one nocturnal feature of SAHS, the AHI, in a group of 41 elderly men with SAHS. All correlations were partially controlled for age, education, depression and subjective sleepiness. AHI significantly correlated with 5 cognitive function tests measuring visuospatial reasoning, memory and psychomotor speed.

In a group of 29 SAHS patients, Cheshire et al (1992) found significant relationships between measures of hypoxaemia, AHI, arousals and cognitive function (all $r > 0.36$, $p < 0.05$). All of these correlations were partial, controlling for age and pre-existing anxiety and depression. Using multiple regression analysis, AHI was the best predictor of performance in terms of visuospatial organisation, sustained attention, visuomotor coordination and vigilance. Sleep fragmentation and hypoxaemia made minor but significant contributions to the multiple regression model. This study suggests that all three important measures of sleep apnoea contribute to relationships and therefore should be measured wherever possible.

Findley et al (1986) examined possible causal relationships using a different approach. 26 sleep apnoeics were divided into 2 groups, with and without hypoxaemia. The hypoxaemic group had lower cognitive performance scores on a number of tests, even when adjusted for age. Correlational relationships were found between the median level of oxygen saturation and overall cognitive dysfunction, but not with the number of desaturations per hour, the number of nocturnal awakenings or movement arousals. However, the hypoxic group were also hypoxic during the daytime, suggesting coexisting lung disease, which would influence the results found. In addition, this study consists of a small sample of patients, making it difficult to rely on the correlational results found.

Studies examining cognitive decrements in snorers and patients with mild SDB have also been performed. A large scale qualitative study (Jennum et al 1994) was performed in 3,323 men from the general community. Subjects self-reported their snoring, sleepiness, memory and concentration problems. No relationships existed between snoring and reported memory or concentration problems, although excessive sleepiness was associated with snoring, memory and concentration problems. This study suggested that the cognitive impairment in snorers may be secondary to sleepiness.

Studies using quantitative measurements and cognitive function tests have also been performed in snorers, although in smaller sample sizes. Studies in snorers (Berry et al 1986, Telakivi et al 1988) found relationships between hypoxia and cognitive function. Berry et al (1986) found that in comparison to normative values, the 46 self-reported snorers (mean AHI=3.2) were only impaired on a few cognitive function scores. In a correlational analysis controlling for age, weight:height ratio and education, the AI, AHI and 4% desaturations all significantly related to the cognitive function measures of intelligence, memory and verbal fluency. The stronger correlational relationships were associated with the nocturnal hypoxia. Although the data was not presented, EEG sleep disruption was also measured, but added nothing



to the existing relationships. The AHI criteria used in the study incorporated a 10% desaturation, which is quite severe, and therefore this study would give a lower than usual AHI. Thus this study population may have also included SAHS patients in addition to the mild SDB patients. Telakivi et al (1988) studied 106 middle aged men from the general community, classified as habitual snorers (46), occasional snorers (38) and never snorers (22), along with 60 age-matched controls, on the basis of a limited sleep study. All underwent a battery of cognitive tests (measuring verbal and performance IQ, memory, psychomotor function and mental flexibility). Hypoxia significantly correlated with memory and spatial orientation decrements in habitual snorers.

Kim et al (1997), in a population study of 841 individuals, examined whether SDB resulted in similar cognitive decrements to those patients with clinically diagnosed SDB. The neuropsychological test battery used measured memory, visuomotor coordination, attention, motor function and mental flexibility, and using principal factor analysis 2 factors were identified: psychomotor efficiency and a memory score. Regression modelling analysis found Log AHI to be associated with psychomotor efficiency, independent of age, gender and educational status (coefficient of Log AHI = -0.07, $p=0.017$). No such relationship was seen with the memory score. The study therefore concluded that in the general adult population, SDB is prevalent and relates to a decrease in psychomotor performance. Measures of hypoxaemia and sleep fragmentation were not measured, and whether or not they would have related to memory score is unknown.

In summary, the general consensus seems to be that measures of hypoxia relate to decrements in cognitive function. Hypoxia may be the best nocturnal predictor or alternatively it may be because many of the above studies did not measure the respiratory events, sleep stages and microarousal frequency. Also hypoxia is a robust physiological measure which can be reproducibly measured, whereas scoring measures of sleep fragmentation are far more variable, making comparisons more difficult. The cognitive tests measuring areas of attention, memory and psychomotor

performance were the most common areas to relate to hypoxaemia in the studies presented here. Such cognitive decrements are important in daily functioning, especially in the vehicle or the workplace. Thus further work examining the predictors of cognitive function is important to pursue.

2.8.3 Relationships with psychopathology

There are limited data on the aetiology of psychopathology. This may be because psychological decrements are only subjectively quantified and therefore lack the strength of more robust physiological tests.

Millman et al (1989) measured depression in sleep apnoeics and found no relationships between the Zung self rating depression scale and AHI or hypoxaemia. The study did not measure sleep fragmentation. Using the Beck depression rating, Watson et al (1985) did find a relationship between AHI and depression. However, it was paradoxical in direction, i.e. the more severe the SAHS disease, the less depressed the individual. Also using Beck's depression rating, Borak et al (1996) found no relationship between sleep and respiratory variables and depression, but did find AHI to significantly correlate with emotional status in terms of anxiety and mental stress.

Smith and Shneerson (1995) studied the possible predictors of quality of life, as measured by the SF-36. Weak but significant relationships were seen between hypoxaemia and the SF-36 dimensions of vitality, general health and physical functioning (all r values < -0.2). The authors speculated that if a measure of sleep fragmentation had been measured, stronger relationships may have been observed.

Daytime sleepiness has also been found to relate to general health in the community as measured by the SF-36 (Briones et al 1996). Daytime sleepiness was measured by the ESS and MSLT, and quality of life using the SF-36. Subjective sleepiness significantly correlated with SF-36 general health, vitality and emotional role (all $r > -0.29$, $p < 0.001$). Objective sleepiness correlated with vitality alone ($r = -0.19$, $p < 0.05$).

Greater relationships may have been observed with subjective sleepiness because of the similarity of subjective measures referring to the recent past. The study concluded that both subjective and objective sleepiness have an effect on quality of life.

In summary, section 2.8 has presented evidence that suggests relationships do exist between nocturnal SAHS variables and daytime function measures, but relationships are frequently only weak or moderate in size, and performed on small study samples. This evidence indicates that there are possible causative effects of nocturnal measures on daytime function, and as such, are worth examining further in this thesis.

Justification for yet another correlational study is discussed in section 2.10 based on the aforementioned studies. Prior to this, the effect of CPAP therapy on daytime function is briefly discussed.

2.9 Improvements in daytime function with CPAP therapy

A further method of identifying causative relationships between nocturnal SAHS variables and daytime function is by examining which daytime measurements improve with CPAP therapy.

Subjective sleepiness as measured by the Epworth sleepiness scale (ESS) has been shown to significantly improve with CPAP therapy in a group of uncontrolled and non-randomised controlled studies (Johns 1992, Hardinge et al 1995, Smith & Shneerson 1995). In addition, Engleman et al (1998) have demonstrated that the ESS significantly improves with CPAP therapy when controlling for the placebo effect in a randomised single blind, placebo controlled crossover study.

The response to CPAP therapy of objective sleepiness has also been studied in uncontrolled trials (Lamphere et al 1989, Bedard et al 1993, Sangal et al 1992b, Poceta et al 1992). Lamphere et al (1989) studied three groups of sleep apnoeics whose sleepiness was measured at baseline, and then after either 1, 14 or 42 nights of

CPAP therapy. Objective sleepiness significantly improved after one night of CPAP therapy, from 3 to 6 minutes, and from 3 to 10 minutes after 14 nights on CPAP. No greater improvement in sleepiness was found after 42 days on CPAP. In this study sleepiness reached normal values after 14 days of CPAP therapy. Bedard et al (1993) also found significant improvements in MSLT with CPAP. Baseline values of 5 minutes, increased to 9 minutes on CPAP. Although a mean sleep onset latency of 9 minutes was significantly lower than the 14 minutes found in the age-matched control group.

Studies have also examined the change in the MWT as an indicator of sleepiness. Sangal et al (1992b) performed a study on 47 patients with disorders of excessive somnolence, of which 26 had sleep apnoea. The SAHS patients underwent the MSLT and MWT at baseline and on therapy. Results found no improvement in the MSLT score with therapy (from 6 to 7 minutes), but did find significant improvements in the MWT score (from 24 to 32 minutes). Therapy in this study consisted of either CPAP or surgery, and treatment efficacy was poor (mean on-treatment AHI of 23/hr slept), so the lack of findings with the MSLT should be interpreted with caution. Poceta et al (1992) found a similar treatment response with the MWT in 24 sleep apnoeics, all treated with CPAP therapy.

Parallel group studies have also been performed using a conservatively treated group of patients for comparison. Engleman et al (1993) compared 21 SAHS patients who were given CPAP therapy, with 16 patients who followed a mild intervention programme of weight reduction, alcohol and sedative avoidance. Sleepiness as measured by the MSLT significantly improved in the CPAP group, although only to a value of 5.5 minutes. This improvement could be due to CPAP therapy or because the CPAP group were significantly sleepier at baseline in this non-randomised study. Following on from this study, Engleman et al (1994a) performed a randomised, placebo controlled crossover study, therefore minimising the influence of treatment order, learning, placebo effects and interindividual variability. 32 patients spent 4 weeks on CPAP and 4 weeks on a placebo tablet, with daytime testing on the last day

of each treatment limb. The study found significant improvements in daytime sleepiness with CPAP therapy. However this sleepiness, as measured by the MSLT, on CPAP was only 7.2 minutes, which is in the 'grey area' of sleepiness, rather than >10 minutes (Carskadon et al 1986). This may be caused by the fact that the mean objective CPAP compliance as measured by mask time (hours the CPAP pressure is within 2cm water of pressure prescribed) was only 3.4 hours per night, and maybe sleepiness can further be improved by greater compliance. In a more recent group of patients, following the same protocol (Engleman et al 1998), the mean MSLT latency on CPAP was 9.2 minutes, which is nearer the normal range, yet the mean effective CPAP use was lower at 2.8 hours per night. Engleman et al (1997a) used the same protocol to perform a placebo controlled crossover study on 16 patients with mild SAHS, defined as having an AHI 5-14.9 and two or more SAHS symptoms. There were no significant improvements in sleepiness, measured either by the ESS or MSLT, although effective CPAP use (mask time) was only 2.8 hours per night, so would not be abolishing all events. Preliminary work by Stradling et al (1998) has used a 'sham CPAP' device as a placebo in a randomised parallel group study. One group of patients were given CPAP at their prescribed pressure to abolish all nocturnal events, whereas the other group were given 'sham' CPAP at a suboptimal pressure. This design aims to overcome the differences in therapies in terms of an obtrusive CPAP device versus a placebo tablet. Preliminary findings indicate that the CPAP user group demonstrate significant improvements in alertness, as measured by a maintenance of wakefulness type test, compared to the 'sham CPAP' group (Stradling et al 1998).

Significant improvements in cognitive function with CPAP have also been found in an uncontrolled study on severe sleep apnoeics (Borak et al 1996). Cognitive function tests measuring concentration and memory (visual, verbal and spatial) improved with CPAP therapy. Bedard et al (1993) also found improvements in cognitive function test scores with CPAP therapy. Verbal memory, attention and constructional abilities improved, to values similar to the age, sex and education-matched control group. Some tests of executive functioning also significantly improved, but not to normative

levels, whilst other executive functioning tasks measuring verbal fluency and mental flexibility demonstrated no improvement with CPAP therapy. Bedard et al (1993) suggest that the cognitive deficits not reversed by CPAP may be caused by hypoxic injury. It could equally be that CPAP may not have been working effectively because hypopnoeas were not measured in this study, or that all night use was not undertaken. In a parallel group study, Engleman et al (1993) found no improvements in cognitive performance with CPAP therapy. Conversely, in the crossover studies (Engleman et al 1994a, 1997a) both the moderate to severe SAHS patients and the mild SAHS patients demonstrated improvements in cognitive performance with CPAP therapy compared to placebo. The moderate to severe SAHS patients demonstrated improvements in vigilance, coding speed and mental flexibility, and the mild group demonstrated improvements in mental flexibility alone. Although the improvements in cognitive function are small in these studies, their randomised crossover design, along with psychometric test familiarisation, minimises the effect of learning, which are likely to influence findings in the parallel and uncontrolled studies (Bedard et al 1993, Borak et al 1996). Studies looking at driving ability using performance measures have also found improvements with CPAP therapy (Findley et al 1989, Engleman et al 1994a, George et al 1997).

Both uncontrolled (Millman et al 1989) and parallel group studies (Derderian et al 1988, Engleman et al 1993) have found improvements in depression scores with CPAP therapy. Improvements in quality of life as measured by the SF-36 (Smith & Shneerson 1995, Jenkinson et al 1997) and function limitations profile (Jenkinson et al 1997) have also been found with CPAP therapy. Redline et al (1998) performed a parallel group study on 97 patients with mild SAHS (RDI 5-30) who were randomly assigned to CPAP therapy or conservative therapy (nasal dilator). Greater treatment responses were found on CPAP therapy for measures of mood and well-being compared to conservative therapy. However, at baseline, the CPAP group demonstrated significantly lower SF-36 physical role scores, and hence greater improvements may be due to regression to the mean and not to CPAP intervention. Engleman et al (1994a, 1997a) found significant improvements in mood and quality of

life scores with CPAP therapy in randomised placebo crossover studies, for both moderate and mild SAHS patients.

This section has provided evidence that CPAP therapy improves daytime function in terms of sleepiness, cognitive function, psychological mood and well-being. Complete reversibility of symptoms to normative values is often not found. Studies have demonstrated that CPAP compliance is well below the length of an average 7 hour night in bed, with values quoted as 3 hours/night in mild patients (Engleman et al 1997a), and 4-5 hours/night in moderately severe sleep apnoeics (Kribbs et al 1993). It is possible that because CPAP therapy is not used all night, normalisation of daytime function is not found.

Patients who are feeling better on CPAP therapy in terms of daytime symptoms, may reduce the hours that they use their machine, or miss out nights altogether and so may not be abolishing all SAHS nocturnal events. Alternatively the incomplete reversibility of symptoms could be due to the fact that nocturnal sleep and breathing parameters only explain part of the variance (Roehrs et al 1989, Poceta et al 1992) in daytime dysfunction and that there are likely to be other unknown causative factors acting on daytime function which are not reversed by CPAP. Or maybe the daytime dysfunction in SAHS is to some extent irreversible, such as permanent hypoxic damage.

2.10 Summary & indications for current investigation

This chapter has demonstrated that patients with the sleep apnoea/hypopnoea syndrome suffer from excessive daytime sleepiness (Roth et al 1980, Whyte et al 1989), cognitive decrements (Greenberg et al 1987, Bedard et al 1991b) and impaired psychological well-being (Cheshire et al 1992, Smith & Shneerson 1995). These daytime effects lead to an increased risk of vehicle accidents (George et al 1987, Findley et al 1988). Studies have also found daytime decrements to improve with CPAP therapy (Engleman et al 1994a, 1997a). Sleep fragmentation studies have

demonstrated that brief arousals from sleep produce sleepiness (Philip et al 1994, Roehrs et al 1994, Martin et al 1996), and impair daytime function (Martin et al 1996).

Correlational studies have described possible causative relationships between the nocturnal factors of SAHS and daytime function. Nocturnal measures have been found to be either not related to sleepiness (Cheshire et al 1992), or to predict less than 13% of the variance in sleepiness (Roehrs et al 1989, Poceta et al 1992). However, all studies are either based on older definitions of arousal (Guilleminault et al 1988b, Roehrs et al 1989, Bedard et al 1991b) or small numbers of subjects (Cheshire et al 1992) or both (Roth et al 1980). The current study therefore used a newer, shorter definition of arousal, large numbers of consecutive patients and newer measures of sleepiness (MWT) and quality of life (SF-36) to determine the nocturnal SAHS factors affecting daytime function. By taking a correlational approach, the current study plans to allow a broad survey of which nocturnal abnormalities predict daytime features of SAHS and therefore hopes to provide some guidance as to who will benefit from CPAP therapy.

Chapter 3

Methods of Measurement

This chapter describes the tests and techniques used in this thesis to diagnose SAHS and to measure daytime function. Polysomnography was used to identify the nocturnal features of SAHS, and to measure objective daytime sleepiness. The psychometric measures used to quantify levels of cognitive performance and psychopathology are also described.

3.1 Polysomnography

After undergoing an initial clinic consultation, patients suspected of having SAHS underwent nocturnal polysomnography. Studies were performed in sound-proofed and electrically-screened bedrooms in the hospital-based Edinburgh sleep centre. Sleep was monitored using electroencephalography (EEG), electro-oculography (EOG) and electromyography (EMG) using bipolar signals from silver chloride surface electrodes. EEG was recorded from 2 scalp sites, Cz/Pz, using the international 10/20 electrode placement system (Cooper et al 1980). 'Mixed' channels consisting of EEG/EOG signals (Cz/Fp1, Cz/Fp2) were also used to monitor frontal EEG. Eye movements were measured from electrodes placed at sites on the outer canthus of each eye and Fp1 and Fp2. This allowed both horizontal and lateral eye movements to be monitored. Submental EMG was recorded using 2 electrodes placed under the chin, on the belly of the genioglossus. In addition, a grounding electrode was placed at Fpz. Leg EMG was measured from electrodes placed over the right and left anterior tibialis. All of these signals were filtered using a high and low bandpass to reduce artefact, along with 50 Hz notch filtering. Electrode impedances of less than 5 kOhms was achieved before the start of each test.

In addition, other nocturnal variables were recorded. Thoracic and abdominal movements were measured by inductance plethysmography, oro-nasal airflow using

thermocouples, and arterial oxygen saturation using pulse oximetry (Ohmeda Biox 3700). Body position was monitored using a mercury switch, in addition to an electrocardiogram, and snoring sounds (using an inbuilt microphone on the bed headboard). All signals were recorded onto a computerised polysomnography system (Compumedics S, Australia) using a 16 channel polygraph configuration.

3.2 Off line analysis

All nocturnal events were manually scored with the exception of oxygen saturation. All events were identified and marked using standard in-lab definitions (Gould et al 1988, Cheshire et al 1992).

3.2.1 Sleep Staging

Sleep was scored from the EEG, EOG and EMG using standard Rechtschaffen and Kales (R & K) (1968) criteria, on an epoch by epoch basis, each epoch length being 30 seconds. This scoring 'window' of 30 seconds creates an averaging of sleep rather than second by second changes in sleep. Rechtschaffen and Kales (1968) classified sleep into 7 stages:

Stage wake : When an individual is wide awake, fast beta activity is seen on the EEG, accompanied by high EMG tone and EOG blinks. Quiet wakefulness consists of alpha (8-11Hz) waves.

Stage 1 : This transient stage displays theta activity (4-7Hz) on the EEG and is characterised by vertex sharp waves. Rolling eye movements are seen on the EOG, often accompanied by a decrease in EMG.

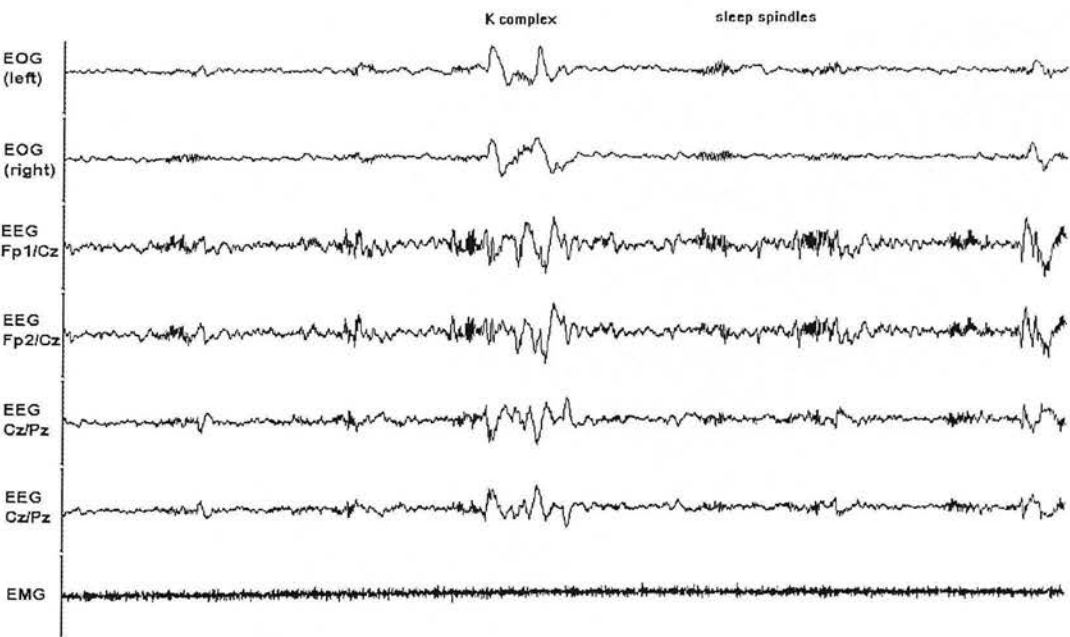
Stage 2 : EEG frequencies are in the theta range (4-7Hz) with the associated EEG phenomenon of sleep spindles and K complexes. Sleep spindles are fast bursts of

activity (0.5-2 seconds) of 12-15 Hz, and K complexes consist of a negative EEG deflection followed by a positive one (Figure 3.1).

Rechtschaffen and Kales (1968) recommend that stage 1 is scored after a page of wake, before stage 2 can be scored. SAHS patients repeatedly wake up briefly, then return straight into stage 2 sleep, rather than passing through stage 1 sleep. Due to this phenomenon, in-house scoring criteria have been made. If an epoch is characteristic of stage 2 (sleep spindles and K complexes), then it is scored as stage 2 rather than stage 1 as suggested by R & K rules (Rechtschaffen and Kales 1968).

Stages wake, 1 and 2 are scored on an epoch if they occupy more than 50% of that epoch.

Figure 3.1; A 30 second epoch of stage 2 sleep, with examples of K complexes and sleep spindles

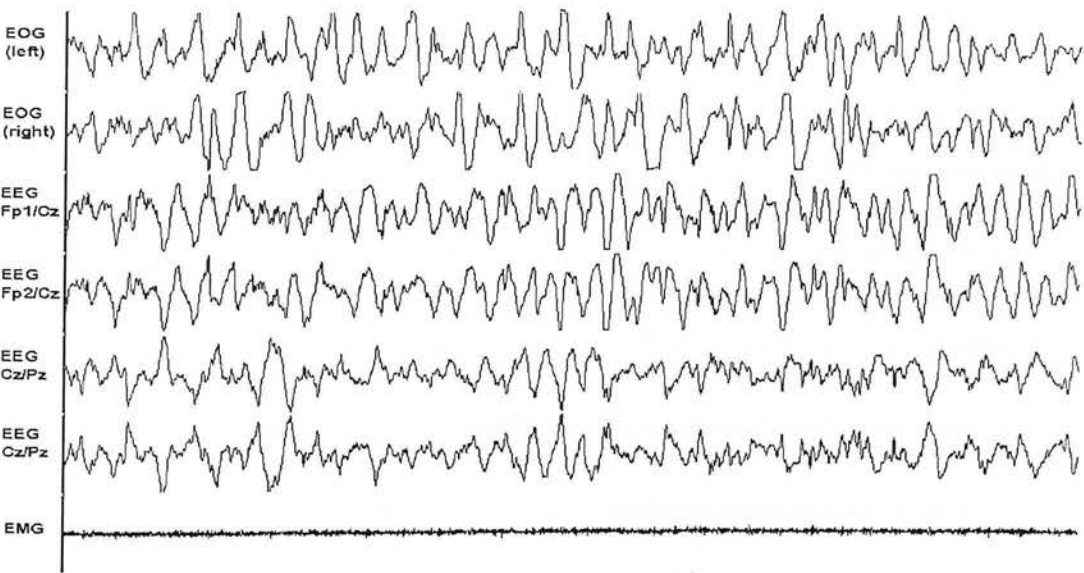


Stage 3 : This transitional stage is scored when 20-50% of an epoch contains delta / slow waves (0-3 Hz) of at least 75 μ V in amplitude.

Stage 4 : This stage is scored when more than 50% of an epoch contains delta waves. Stages 3 and 4 are often collectively called slow wave sleep (SWS) or delta sleep (Figure 3.2). The quantity of SWS is often reduced or even omitted in a patient with moderate or severe SAHS. The repetitive arousals from sleep prevent a patient from passing from the lighter sleep stages of 1 and 2, through to stages 3 and 4, before another arousal occurs.

Stages 1 to 4 can be grouped together as non-REM sleep.

Figure 3.2; A 30 second epoch of stage 4 / slow wave sleep

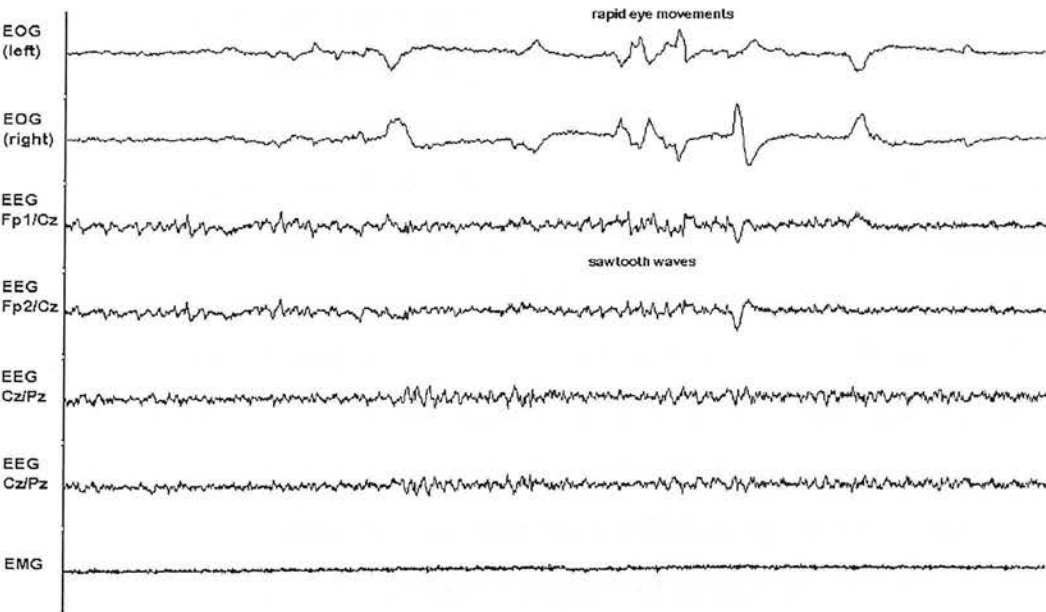


REM sleep : This sleep stage has similar EEG frequencies to stage 1 sleep, along with characteristic waves resembling saw teeth. The EMG tone is at its minimum except for phasic bursts of higher activity. Rapid eye movement activity is seen on the

EOG, giving this sleep stage its characteristic name (Figure 3.3). These eye movements often occur in bursts, and are not always present on each epoch. If the epoch fulfils the other characteristics of REM sleep, it can be scored as such, providing a rapid eye movement has occurred within the last 3 minutes.

Movement time : This is scored in a study when the EEG and EOG channels are obscured by large movement / equipment artefacts. This does not include large bursts of muscle activity seen when a person wakes up from sleep.

Figure 3.3; A 30 second epoch of REM sleep, with characteristic eye movements, saw tooth waves and low amplitude EMG.



3.2.2 Respiratory events

The sleep apnoea/hypopnoea syndrome is characterised by 2 types of respiratory event which are scored routinely.

An **obstructive apnoea** is defined as a complete cessation of airflow for a minimum of 10 seconds, associated with continued thoracoabdominal movement (Guilleminault et al 1978) (Figure 3.4).

A **hypopnoea** is defined as a reduction in thoracoabdominal movement of at least 50% for a minimum of 10 seconds (Gould et al 1988) (Figure 3.5). This definition does not require the coexistence of either arousals or oxygen desaturations.

The total number of apnoeas plus hypopnoeas is calculated, and divided by total sleep time (TST) to give the apnoea + hypopnoea index (AHI).

3.2.3 Arousals

Using R & K scoring rules, only awakenings of greater than 15 seconds are noted. In sleep apnoea, patients frequently have brief arousals (<15 seconds) from sleep, on termination of respiratory events. These 'microarousals' alter sleep quality and are therefore important. Microarousals may be scored from the EEG/EMG polysomnography channels. In this thesis, the in-house Cheshire definition was used (Cheshire et al 1992) which has been validated against other microarousal definitions (Martin et al 1997c). An arousal was defined as a return to alpha or theta for at least 1.5 seconds associated with a transient rise in EMG, however brief (Figures 3.4 & 3.5). The total number of arousals were divided by TST to give an arousal frequency per hour slept. In this thesis, no distinction was made between 'spontaneous' and respiratory-related arousals. Arousals that are classified as 'spontaneous' are by definition not associated with a scored hypopnoea or apnoea. But they may be associated with a snore or a period of flow limitation. Therefore defining an arousal as 'spontaneous' and excluding it from further analysis would overlook the fact that the arousal may have an unseen physiological cause, not detected by standard measurement techniques. 'Spontaneous' arousals can cause sleep fragmentation, regardless of their cause.

Figure 3.4; A 120 second epoch of two obstructive apnoeas, with associated arousals and oxygen desaturations

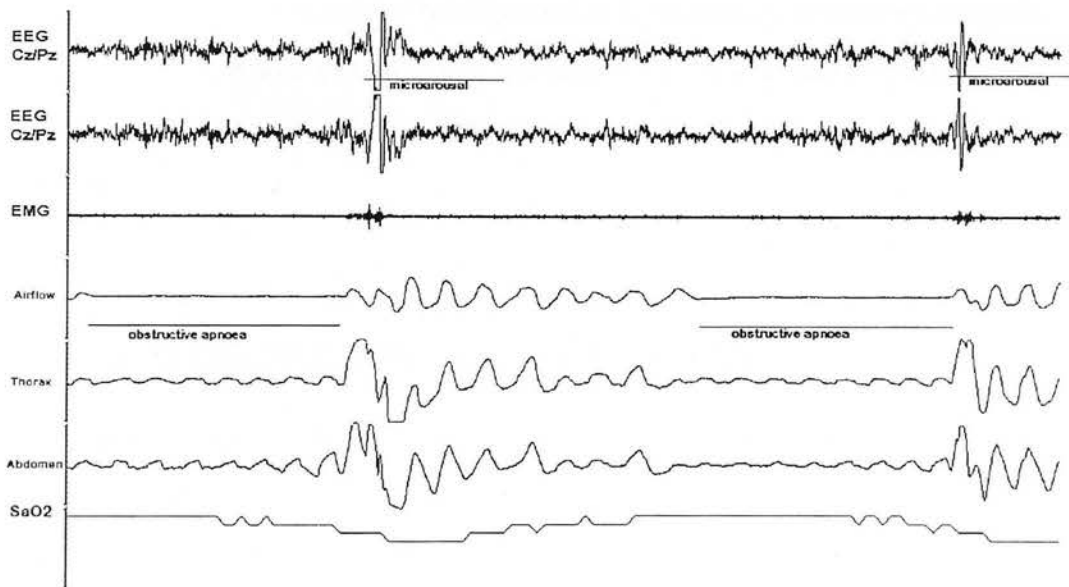
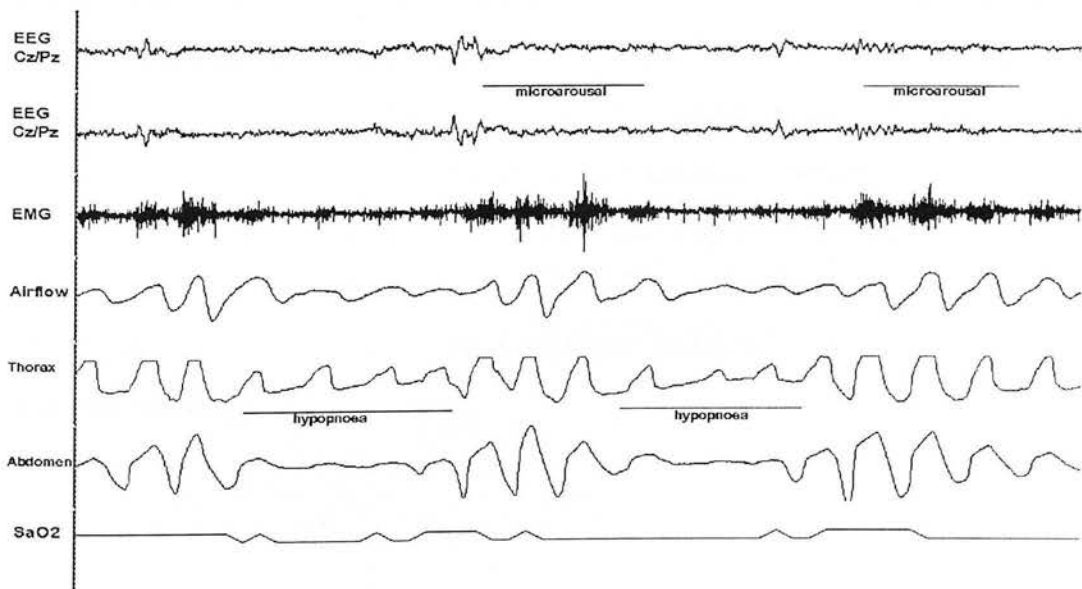


Figure 3.5; A 60 second epoch of two hypopnoeas with associated arousals from sleep



3.2.4 Hypoxaemia

The frequency of oxygen saturation (SaO_2) dips of 2, 3 and 4% from the running peak, along with minimum overnight saturation were analysed using an automatic desaturation detection algorithm (Compumedics S, Australia). In addition, oxygen saturation whilst awake was measured manually from the oximetry channel prior to sleep onset on the overnight polysomnography (saturation trace shown on Figures 3.4 and 3.5).

3.3 Reproducibility of polysomnographic scoring

Although nocturnal SAHS events are all scored according to strict criteria, there is still a subjective element in marking such events. This is likely to be due to variability in the quality of overnight recordings, along with the unpredictability in the occurrence of respiratory events, arousals and changing sleep patterns found in SAHS compared with a normal text book pattern. Therefore scoring reproducibility for arousals, respiratory events and total sleep time (TST) was tested.

Twenty overnight polysomnography records were randomly selected for reanalyses. Ten of these records were originally scored by the senior lab technician and ten by myself, to test inter-rater and intra-rater reproducibility, respectively. Records were rescored at least 12 months after the first score with patient details and original results unknown to myself. The results of the inter- and intra-rater reproducibility correlations are shown in Table 3.1. Both inter- and intra-rater reproducibility correlations were high, with r values ≥ 0.88 ($p \leq 0.001$). In addition, the mean differences between score 1 and score 2 are shown in Table 3.1, again demonstrating high reproducibility.

Table 3.1; Reproducibility of AHI, arousal frequency and TST.

Nocturnal Variable	Score 1 mean (SD)	Score 2 mean (SD)	r-value	mean(SD) score difference (score 1-score 2)
Inter-rater reproducibility				
AHI (per hr slept)	47.5 (38.3)	51.0 (38.4)	0.99***	-3.5 (3.6)
Arousals (per hr slept)	54.9 (35.4)	58.9 (35.8)	0.88**	-4.0 (8.5)
TST (mins)	322.1 (88.9)	318.7 (87.2)	0.96***	3.4 (9.6)
Intra-rater reproducibility				
AHI (per hour slept)	49.3 (30.9)	52.1 (30.9)	0.95***	-2.8 (3.9)
Arousals (per hour slept)	63.6 (29.1)	60.7 (30.4)	0.88**	2.9 (7.9)
TST (mins)	347.9 (90.1)	343.9 (92.3)	0.96***	4.0 (11.0)

** p<0.01; ***p<0.001

Figures 3.6 (a) and (b) graphically display the differences between the two arousal scores (with pooled data from all 20 rescored records). The scatter plot (Figure 3.6 a) demonstrates a close relationship between the first and second arousal scores. The Bland Altman plot, shown in Figure 3.6 (b), better demonstrates the differences between first and second arousal scores. The mean (SD) % error in arousal frequency between the two scores, using score 1 as the ‘standard’ was -3.7(22) per hour slept. This mean error between arousal scores is generally small, although can be relatively large at the milder end of the disease spectrum, where less events are scored.

Figure 3.6 (a); A scatterplot of the relationship between the first and second arousal frequency score for all 20 rescored records ($\rho=0.90$, $p<0.0001$). Also displayed on the graph is the line of identity

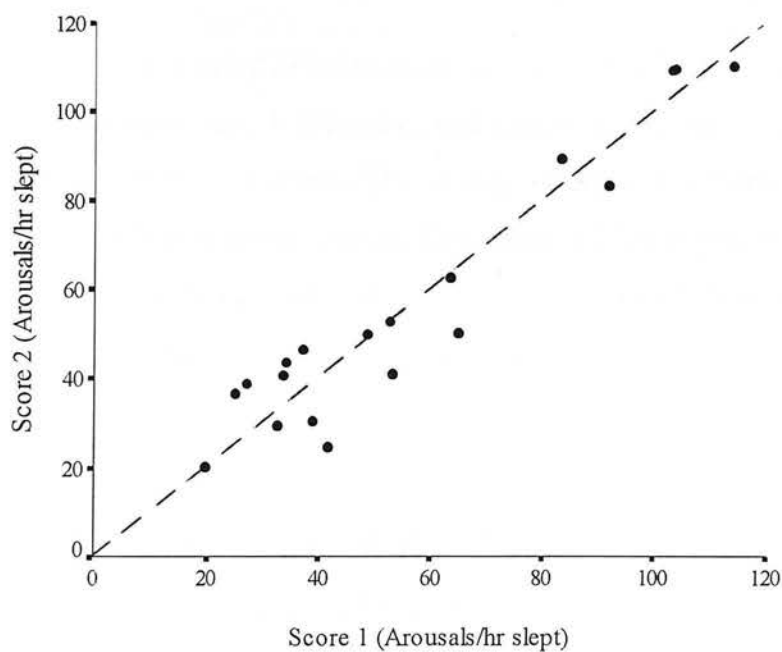
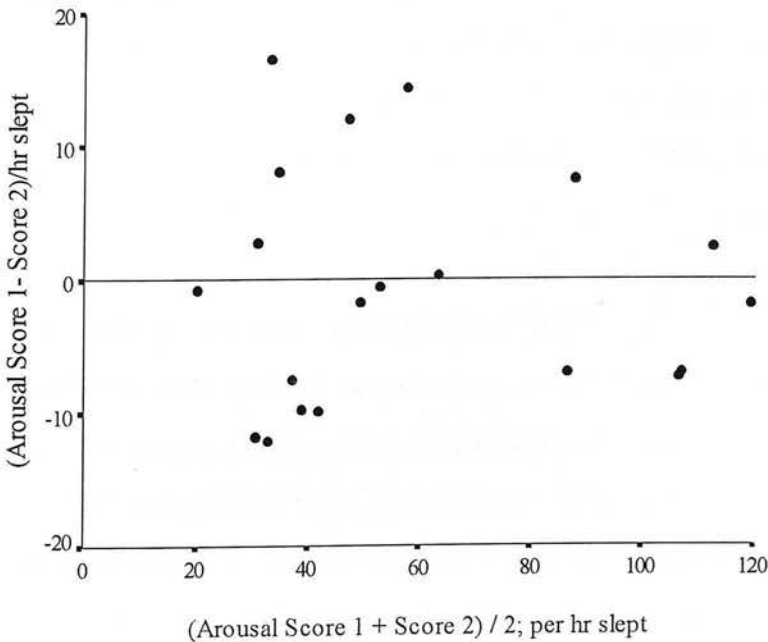


Figure 3.6 (b); A Bland Altman plot demonstrating relationships between the first and second arousal frequency scores



Martin et al (1997c) examined arousal reproducibility by correlational analysis, and as demonstrated above, found high inter-rater reproducibility (all $r > 0.96$, $p < 0.0001$). The study by Martin et al (1997c) and the current analysis demonstrate that arousals can be scored with reasonable reproducibility for a complex physiological measurement.

As anticipated, scoring of the arousals was the least reliable of the 3 nocturnal measures studied here. It is possible that arousal scoring has the greatest variance because it requires a minimum EEG change of only 1.5 seconds in duration. In comparison, respiratory events and sleep stage scoring require longer periods of 10 and 15 seconds, respectively. Also, by definition, arousals have a greater probability of occurring, thus increasing their chances of scoring error.

3.4 Measuring daytime sleepiness

Daytime sleepiness (Section 2.2) can be measured either by subjective questionnaires or objectively using polysomnographic variables.

3.4.1 Subjective measures

Stanford Sleepiness Scale (SSS) (Hoddes et al 1973)

This is a self-completed 7 point scale, where a patient has to rate their level of sleepiness at that particular moment in time. Sleepiness is rated from feeling wide awake (1) through to struggling to remain awake (7). This scale therefore measures instantaneous sleepiness.

Epworth Sleepiness Scale (ESS) (Johns 1991)

This self-completed scale asks a patient to rate their sleepiness in recent times in 8 everyday situations. The 8 everyday situations were carefully selected by Johns (1991) to allow for people's differing daily routines. Rather than just asking if a patient feels sleepy, the ESS provides 8 real-life situations in which a patient has to rate their level of sleepiness. This provides some guidance and standardisation for quantifying

sleepiness. These real-life situations differ in their soporific nature, with some being highly soporific, such as ‘sitting quietly after lunch without alcohol’, or ‘lying down to rest in the afternoon’, and others are non-soporific, such as ‘sitting and talking to someone’ or ‘in a car whilst stopped for a few minutes in the traffic’. In these non-soporific situations one would expect only a sleepy person to fall asleep. Sleepiness is rated using a four-point ordinal scale from (0) would never doze, (1) slight chance of dozing, (2) moderate chance or (3) a high chance, therefore allowing scores to range from a minimal level of sleepiness of 0, to a maximum level of sleepiness of 24. An example of this scale is shown in Chapter 4 which describes a validation study on the ESS.

3.4.2 Objective measures

Daytime sleepiness was measured objectively using both the multiple sleep latency test (MSLT) (Carskadon et al 1986, Thorpy 1992) and the maintenance of wakefulness test (MWT) (Poceta et al 1992). Both of these tests evaluate daytime sleepiness by physiologically measuring an individual’s tendency to fall asleep. Very few studies have run both the MSLT and MWT on the same day (Sangal et al 1992a & 1992b, Martin et al 1996 & 1997b). In this thesis both tests were performed on the same day, to compare these objective measures with each other, and against the battery of psychometric measures (Chapter 6).

The MSLT and the MWT require polysomnographic recording of the EEG, EOG, and EMG (electrode placement as described in Section 3.1). Tests were performed at evenly spaced intervals across the test day to account for circadian differences in sleepiness. For the MSLT, naps were run at 10.00, 12.00, 14.00 and 16.00. The patient was asked to lie comfortably on a bed in a quiet, dark room and instructed to “close their eyes and try and sleep” for 20 minutes. For the MWT, naps were run at 11.00, 13.00, 15.00 and 17.00. This time the patient was seated comfortably upright on the bed, with the head and neck supported and instructed to “try and stay awake” for forty minutes. Patients were also instructed not to use any extraordinary measures

to promote alertness, such as singing, exercising or reading. The room was quiet and dimly lit (to a set level) for each MWT.

Original MSLT guidelines (Carskadon et al 1986) for the research version of the test recommended that each nap is terminated after the first three consecutive epochs of stage 1 sleep, or a single epoch of any other sleep stage. In this thesis a modified definition of test termination to the first epoch of any sleep stage, including stage 1, was used for both the MSLT and MWT. This modified definition was used for two reasons. Firstly, this allows for SAHS patients who have frequent respiratory related arousals at sleep onset. These patients may not be capable of maintaining stage 1 for 3 consecutive epochs. Secondly, due to 8 tests being performed across the day, this short test termination prevents patients gaining additional sleep in the daytime. To prevent premature termination of these naps, in many cases 2 consecutive epochs of R & K sleep were noted by myself before the test was terminated. If no sleep was observed, the MSLT was terminated after 20 minutes, and the MWT after 40 minutes.

Scoring of these tests was performed on a separate day. Sleep onset latency (SOL) is defined as the elapsed time from lights-out to the first epoch of any sleep stage, including stage 1 sleep (Thorpy 1992). The sleep onset latencies across the day are averaged for the MSLT and MWT, respectively, to provide two outcome measures of objective daytime sleepiness.

3.4.3 Reproducibility of MSLT & MWT scoring

All 1,200 MSLTs and MWTs were scored by myself. To determine intra-rater reproducibility of sleep onset latency scoring, 20 sets of MSLTs and MWTs (160 records) were rescored by myself, at least 12 months after the original scoring. The records were chosen at random by a colleague and I was blind to the patient information and original score in each case. Reproducibility correlations for the mean SOL of each hourly test was high, as were the overall means (Table 3.2). In addition, the mean differences between score 1 and score 2 are in Table 3.2, again demonstrating high reproducibility.

Table 3.2; Reproducibility of MSLT and MWT sleep onset latency scoring*

Daytime Nap	Score 1 mean (SD)	Score 2 mean (SD)	r-value	mean (SD) score difference (score 1 - score 2)
10:00 MSLT (mins)	13.0 (6.1)	13.7 (6.3)	0.97	-0.7 (1.4)
12:00 MSLT (mins)	10.4 (6.0)	10.9 (6.2)	0.98	-0.5 (1.1)
14:00 MSLT (mins)	7.7 (5.6)	8.2 (5.7)	0.98	-0.5 (1.1)
16:00 MSLT (mins)	9.7 (5.9)	10.0 (5.8)	>0.99	-0.3 (0.8)
mean MSLT (mins)	10.2 (5.1)	10.7 (5.1)	0.99	-0.5 (0.8)
11:00 MWT (mins)	30.5 (11.1)	30.6 (10.8)	>0.99	-0.1 (0.9)
13:00 MWT (mins)	21.7 (12.4)	22.2 (12.4)	>0.99	-0.5 (0.9)
15:00 MWT (mins)	25.2 (12.1)	26.0 (12.1)	0.98	-0.8 (2.5)
17:00 MWT (mins)	25.2 (14.7)	25.0 (14.3)	0.96	0.2 (4.3)
mean MWT (mins)	25.4 (10.5)	25.9 (10.6)	>0.99	-0.5 (0.9)

* r values all $p < 0.0001$

3.5 Psychometric Measures

A range of daytime function measures were used in this thesis. Daytime testing was performed after a normal night's sleep at home, within one month of the overnight polysomnography. Patients were instructed to withdraw from caffeine on the evening prior to daytime testing, and throughout the test day, decaffeinated drinks were provided. All tests were applied at the same time of day in all subjects.

General patient information and body measurements were taken for each patient. These included anthropometric measurements of Body Mass Index ($BMI = \text{weight} / [\text{height}^2]$), collar size (at the level of the cricothyroid membrane) and waist circumference (midway between the lower rib margin and the superior anterior iliac spine). Information concerning past medical history, medications, years of education and smoking and drinking habits were also taken.

3.5.1 Self-ratings of daytime function

Self-administered questionnaires were given to SAHS patients in the morning of the daytime session. Patients were shown how to complete the questionnaires, and then left alone to fill them in, with any queries answered once all were attempted.

Short Form 36 Health Survey (SF-36) (Ware & Sherbourne 1992)

This generic questionnaire measures functional status, well-being and health perception. The SF-36 consists of 36 questions grouped into 8 multi-item dimensions. Raw scores are transformed to create minimum scores of 0 through to the best possible health status of 100%. Responses given are either yes/no, frequency responses or true/false statements. The main 8 domains of the survey are described in Table 3.3.

Table 3.3; SF-36 Domains

SF-36 Domain	No of questions	Area of quality of life
Physical Functioning	10	The level by which health limits a range of physical activities
Social Functioning	2	The effect that physical / emotional problems have on social activities
Vitality	4	Refers to how energetic one is feeling
Role Limitations - physical	4	The effect physical problems have on the range and extent of work
Role Limitations - emotional	3	The effect emotional problems have on the range and extent of work
General Health	5	Refers to an individuals rating of their own health & how it compares to others
Bodily Pain	2	Refers to the severity of pain and its effect on daily life
Mental Health	5	Refers to the degrees of nervousness, happiness, calmness, sadness

An additional dimension known as health transition remains unscored. This single item compares health now to one year ago. Recently two principal components were extracted from the SF-36. These are known as the physical components summary (PCS) and the mental components summary (MCS). These summary scores reduce the chance of Type 1 error due to multiple comparisons.

Hospital Anxiety and Depression (HAD) Scale (Zigmond & Snaith 1983)

This mood scale measures levels of anxiety and depression. 7 statements measure anxiety levels (e.g. I can sit at ease and feel relaxed) and 7 measure depression (e.g. I feel cheerful). Patients have to rate their agreement with each statement on a 4 point

scale (0-3), to reflect the frequency or intensity of agreement. Rating scores for anxiety and depression therefore range from a minimum of 0 to a maximum of 21. Scores of 11 or over are considered clinically significant cases of anxiety or depression, and scores between 8 and 10 are considered suspicious cases.

Nottingham Health Profile (NHP) Part 2 (Hunt et al 1984)

This well-being questionnaire provides a list of health problems found in daily living. These are subdivided into problems at work, in the home, social life, sex life and hobbies. For example, problems include 'I'm getting irritable with the people I live with' and 'I'm having difficulty concentrating at work'. Patients answer yes/no to each statement. The outcome score ranges from a minimum of 0 (reflecting no impairment) to a maximum decrease in well-being of 20.

Symptoms Questionnaire

Symptoms of sleep apnoea were measured using an in-house questionnaire (Appendix A). Patients rated the frequency of symptoms on a 5 point scale from never, through to every night. Symptoms measured were heavy snoring; choking during the night; witnessed breathing pauses; difficulty staying asleep at night; unrefreshing sleep; daytime and evening napping and feeling sleepy and falling asleep whilst driving.

Eysenck Personality Scale (Eysenck et al 1985)

This revised scale contains 48 yes/no questions, that relate to the 3 personality domains of neuroticism, psychoticism, extraversion, plus a lie scale. Questions include: 'Would you call yourself a nervous person?' (neuroticism domain), or 'Are you rather lively?' (extraversion domain).

3.5.2 Cognitive Performance Tests

Cognitive tests were performed in the afternoon of the daytime testing day.

Digit Symbol Substitution (Wechsler 1981)

Digit symbol is a subtest of the Wechsler Adult Intelligence Scale - revised version (WAIS-R). It measures coding speed. This pen and paper test requires the patient to write appropriate characters underneath numbers by referring to a given code key. Patients are initially given a practice trial of 7 substitutions. Patients then have 90 seconds to complete as many substitutions as possible in the order presented on the sheet (Figure 3.7a). The number of correct substitutions in 90 seconds is noted and converted into a scaled score.

Block Design (Wechsler 1981)

This subtest of the WAIS-R measures visuospatial ability. In this test patients have to reproduce printed designs using coloured blocks. Each test is to be completed as quickly as possible, with bonus points available for quick completion, although any error in the design results in zero points. Time to completion is measured and converted into a scaled score (Figure 3.7b).

Performance IQ

The scores from the WAIS-R subtests, digit symbol and block design, are scaled according to Wechsler (1981). These scaled scores are then added together and multiplied by 2.5 to give a scaled score estimate. This value is then converted into an estimated performance IQ value using age-specific tables (Wechsler 1981).

National Adult Reading Test (NART) (Nelson 1982b)

To try and identify if intellectual abilities have changed with a disease state, a premorbid measure is required. Current reading ability and previous familiarity of certain words is hypothesised to be a well-maintained skill even in patients with dementia, for example (Nelson & O'Connell 1978, O'Carroll et al 1987). Such a test can be used to estimate a premorbid level of intelligence. The national adult

reading test (NART) was devised to estimate this pre-morbid level of general intellectual functioning. It consists of a list of 50 words which are slowly read out loud by the subject whilst pronunciation is noted by the examiner. All the words on this list are phonetically irregular words (example in Figure 3.7c) and can only be pronounced correctly if the subject has previous familiarity with them. Words are listed in increasing order of difficulty. The total number of incorrect pronunciations are then totalled and converted using Nelson's (1982b) tables to provide an estimate of premorbid intelligence levels. Nelson (1982b) demonstrated the NART IQ is highly correlated with the WAIS IQ in normal subjects.

IQ Decrement (Langan et al 1991)

A measure of the change in IQ since early adult life can be estimated by subtracting the WAIS-R performance IQ from the premorbid NART IQ.

Paced Auditory Serial Addition Task (PASAT) (Gronwall 1977)

This test measures attention and information processing. Patients listen to a tape recording of single digit numbers presented at a rate of one number every 4 seconds. The patient has to add up the last two numbers called out and give the answer. For example, if the numbers presented were 2 then 3 the answer would be 5, if next number was 7 then the answer would be 10 ($3 + 7$), and if the next number was 9, the answer would be 16 ($7 + 9$), and so on. The test consists of 61 consecutive numbers, and is read out once at a 4 second presentation rate, and then again at a 2 second presentation rate. Outcome scores on both runs are the total correct additions.

Trail Making A & B (Reitan 1958)

This is a two part pen and paper test. Twenty five circles are randomly printed on a side of A4 paper. In part A of the test, these circles are numbered 1-25. The patient is required to draw connecting lines between the circles in numerical order. In part B, half of the circles are numbered 1-13, and the others contain letters A-L. This time the patient has to connect consecutively numbered and lettered circles by alternating between the two, e.g. 1 to A to 2 to B etc. In both tests patients are required to

complete the trials as quickly as possible, and scoring is based on time to completion. If an error occurs, this is pointed out by the examiner and must be corrected. Both parts measure orientation and attention, and part B also measures mental flexibility (Figure 3.7d).

Simple Unprepared Response Time (SURT) Task (Wilkinson & Houghton 1982)

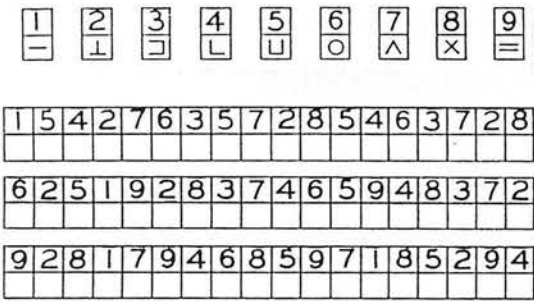
This is a 10 minute computerised reaction time task. Patients sit in front of a black computer screen. At random, between 1 and 10 second intervals, a white square appears in the centre of the screen. When each visual stimuli appears, patients respond by pressing the keyboard space bar as quickly as possible. Outcome measures from this test include mean reaction time, number of false responses and number of gaps (when reaction time response >1 sec). This test measures information processing time and attention.

Steer Clear (Findley et al 1989)

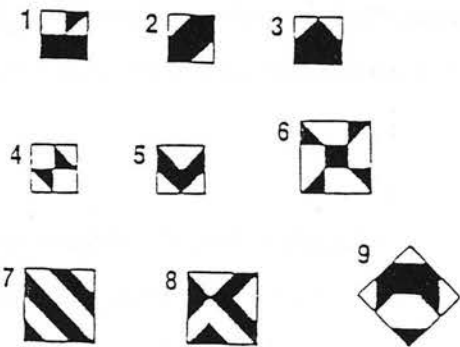
This is a computerised vigilance task measuring attention and reaction time. In this task a computer screen displays a bird's eye view of a two lane motorway. The patient is in control of a vehicle moving along the motorway. Cows intermittently appear on the motorway moving towards the oncoming vehicle. To avoid hitting the cows, the patient must press the keyboard spacebar for the vehicle to change lanes. The test is long and monotonous, being run for 30 minutes in a dimly lit quiet room. On three occasions during the test, the cows disappear for 2 minutes, further testing attention span. The outcome score is the percentage of cows hit by the car within the 30 minute time period.

Figure 3.7; Examples of Psychometric Measures

(a) Digit Symbol



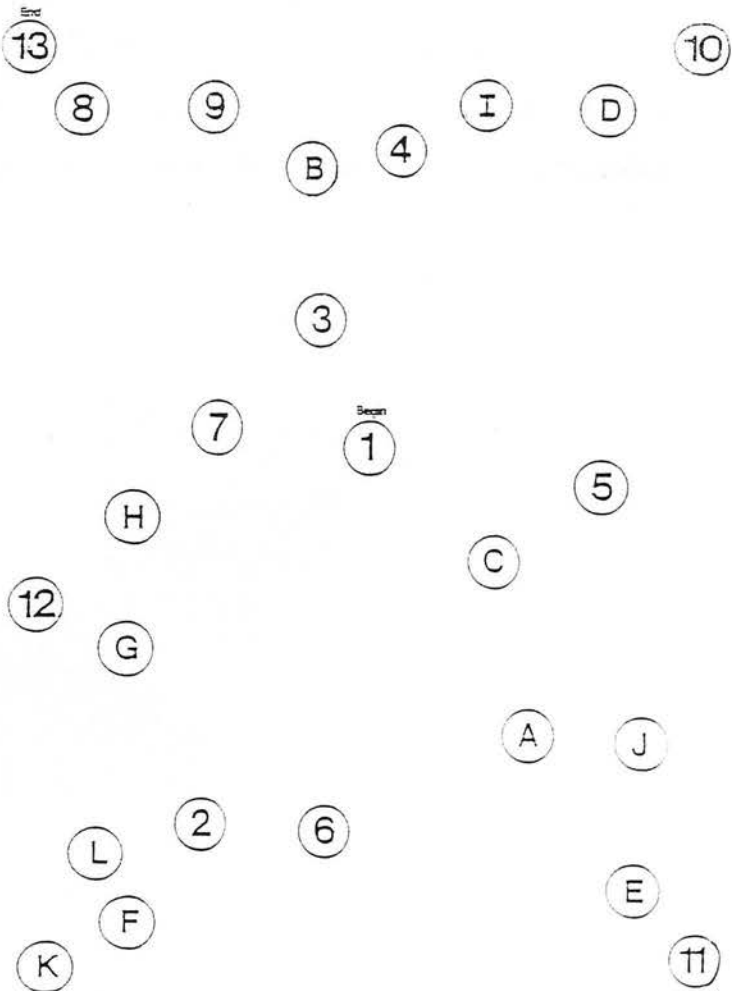
(b) Block Design



(c) NART

SUPERFLUOUS
SIMILE
BANAL
QUADRUPED
CELLIST
FACADE
ZEALOT
DRACHM
AEON
PLACEBO
ABSTEMIOUS
DETENTE

(d) Trail Making B



3.6 Summary

The polysomnography and off line analysis methods described in this chapter are the standard procedures used in the Edinburgh sleep centre. Any deviation from the normal procedures will be mentioned in the methods section of the relevant chapters, otherwise all methods described in the remaining chapters will be referred back to this chapter.

I have summarised each of the daytime function measures I used in the following experiments. These particular tests were chosen for a number of reasons. Firstly, to provide a broad range of daytime function measures. Previous studies have tended to focus on single areas of daytime function (Roehrs et al 1989, Poceta et al 1992), whereas I wanted to include a range of measures to allow for comparisons between them. Secondly, I wanted to incorporate similar tests as used in the previous correlational study from the Edinburgh sleep centre (Cheshire et al 1992), with the addition of the quality of life and sleepiness scales and the MWT, which were not used then. Thirdly, other studies from the Edinburgh sleep centre have demonstrated improvements in these daytime function measures with CPAP therapy (Engleman et al 1994a), and changes in these measures as a result of experimental sleep fragmentation (Martin et al 1996).

Chapter 4

The Epworth Sleepiness Scale (ESS): Patient versus Partner Assessments

4.1 Introduction

As discussed in the introduction to this thesis, excessive sleepiness is the most common daytime feature of the sleep apnoea/hypopnoea syndrome (Whyte et al 1989). Daytime sleepiness frequently interferes with an individual's daily routine. In particular, sleepiness may lead to problems whilst driving, with studies reporting sleep apnoeics to have an increased risk of vehicle accidents compared to control subjects (George et al 1987, Findley et al 1988). These detrimental consequences to the patient, and other road users, highlights the need to quantify this excessive daytime sleepiness.

The multiple sleep latency test (MSLT) (Carskadon et al 1986) and the maintenance of wakefulness test (MWT) (Mitler et al 1982) are commonly used objective measures of daytime sleepiness (Section 3.4.2). These tests measure a patient's ability to fall asleep by monitoring physiological sleep onset. However, these tests are labour intensive and expensive to conduct, and are therefore hard to justify in routine clinical practice.

More simply, self-reporting questionnaires assessing sleepiness have been devised, which are cheap and easy to use. The Epworth sleepiness scale (ESS) (Johns 1991; Figure 4.1) is the most widely used scale to assess recent sleepiness in SAHS patients (Section 3.4.1). Johns (1991) examined the discriminative validity of the scale and found that ESS scores differed significantly between normal controls and groups of patients with a variety of sleep disorders. ESS scores ≤ 10 were considered normal, with a mean ESS value of 4.6 reported in a group of 72 middle aged normal subjects (Johns & Hocking 1997). The ESS score significantly correlated with the respiratory disturbance index ($r=0.4$, $p<0.001$), and the minimum oxygen saturation level

($r = -0.5$, $p < 0.001$) in SAHS patients (Johns 1991, 1993). These results suggest that the ESS score might predict SAHS disease severity to some extent.

The ESS is routinely used in the Edinburgh sleep centre, and both the patient and their witnessing partner are asked to independently rate the patient's sleepiness using this scale. Anecdotally, there is frequently a discrepancy between a patient's and their partner's ESS assessment, and between ESS scores and the severity of nocturnal SAHS symptoms. Therefore, the first aim of this study was to compare the patients' and partners' assessments of the patient's sleepiness, using the Epworth sleepiness scale. The second aim was to determine if either the patient's or their partner's rating on the ESS is a better predictor of SAHS disease severity.

Figure 4.1; The Epworth Sleepiness Scale (Johns 1991)

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

Scale

- 0 = would *never* doze
- 1 = *slight* chance of dozing
- 2 = *moderate* chance of dozing
- 3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g. a theatre or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, when stopped for a few minutes in the traffic	_____

Thank you for your co-operation

4.2 Methods

4.2.1 Study Design

This study was retrospective in design, collecting questionnaire and sleep study data from a consecutive group of patients referred to the sleep centre with symptoms of the sleep apnoea/hypopnoea syndrome. An in-house sleep/wake questionnaire was sent to patients to complete prior to their initial outpatient consultation (Appendix B). This patient questionnaire includes sections on past medical history, social background, sleep hygiene and sleep disorder symptoms. A separate questionnaire was sent to the partner (or parent of a young individual) with questions on the patient's caffeine and alcohol intake, napping habits, general daytime sleepiness, sleepiness whilst driving, and personality changes. Both the patient and partner questionnaires also contain Epworth sleepiness scales (ESS) for the patient and partner to independently rate the patient's sleepiness. These questionnaires were reviewed in the clinic by a physician. If answers were incomplete or incorrectly filled in, patients and partners were helped to complete the questionnaire. From the questionnaire details, referral information and the clinic consultation, subjects suspected of having SAHS underwent diagnostic polysomnography to measure sleep and respiratory variables. The nocturnal variables defined and measured followed the standard laboratory protocol, as described in Chapter 3. The only exception to this was that polysomnography was performed on paper chart recorders (SLE) prior to the installation of the computerised system. From the overnight polysomnography, the apnoea + hypopnoea index (AHI), arousal frequency and the minimum oxygen saturation were calculated.

From the ESS, a total score is calculated by adding up the scores from the 8 real-life situations (Figure 4.1). Scores range from a minimum sleepiness score of 0, to a maximum sleepiness score of 24. In addition, the minimum ESS (minESS) and the maximum ESS (maxESS) values for each couple were analysed.

4.2.3 Statistics

Patient and partner ESS scores were normally distributed, and therefore the mean difference between them was compared to zero using a 2-tailed paired t-test.

Relationships between nocturnal sleep and breathing variables and ESS scores were evaluated by Spearman rank correlations. Statistical significance was accepted as $p < 0.05$. All analysis was performed using SPSS+PC. The statistically significant results in this chapter are represented in the tables in bold type for clarity.

4.3 Results

4.3.1 Study population

This retrospective study collected data from 103 patients (87 men) (Table 4.1) and their witnessing partners.

Table 4.1; Patient Details (n=103)

Measurements	mean (SD)	Range
Age (years)	48 (13)	14 - 89
BMI (kg/m ²)	30 (5)	21 - 50
AHI (per hour slept)	28 (22)	0 - 95
Arousal frequency (per hour slept)	25 (18)	2 - 101
Min Sat (%)	84 (12)	11 - 96

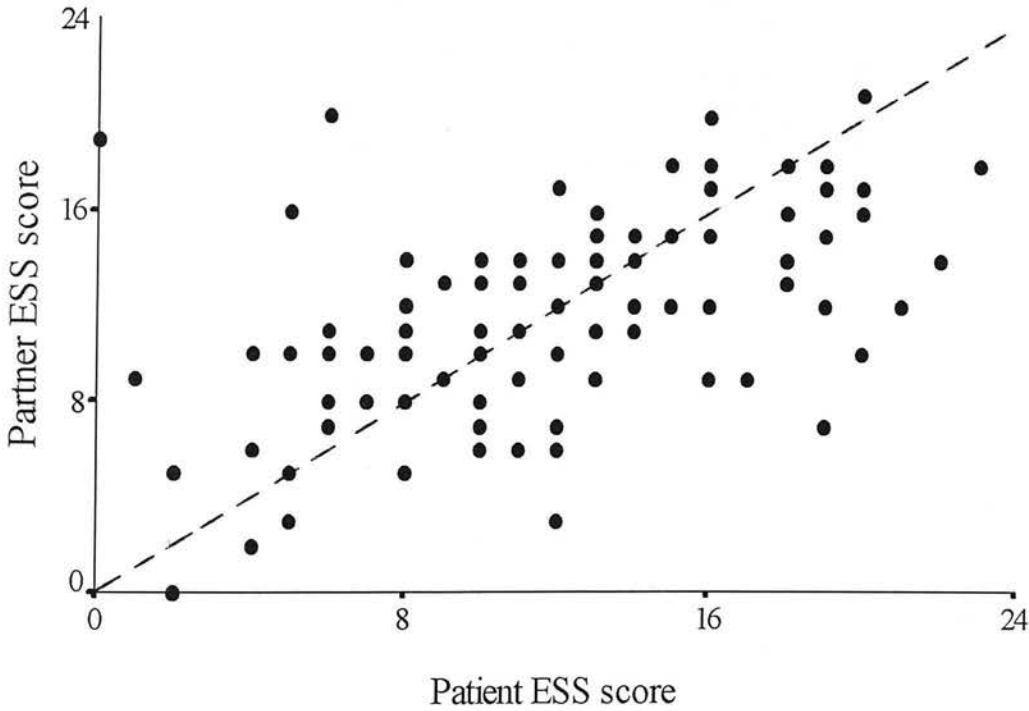
BMI=Body mass index; AHI=Apnoea+hypopnoea index; Min sat=Minimum oxygen saturation

All patients were referred because of possible SAHS. As can be seen from the AHI range in Table 4.1, not all individuals had SAHS. However, all are included in the initial analysis, as the second aim of the study was to examine patient and partner ESS scores as possible predictors of SAHS severity.

4.3.2 Comparisons between patient and partner mean ESS scores

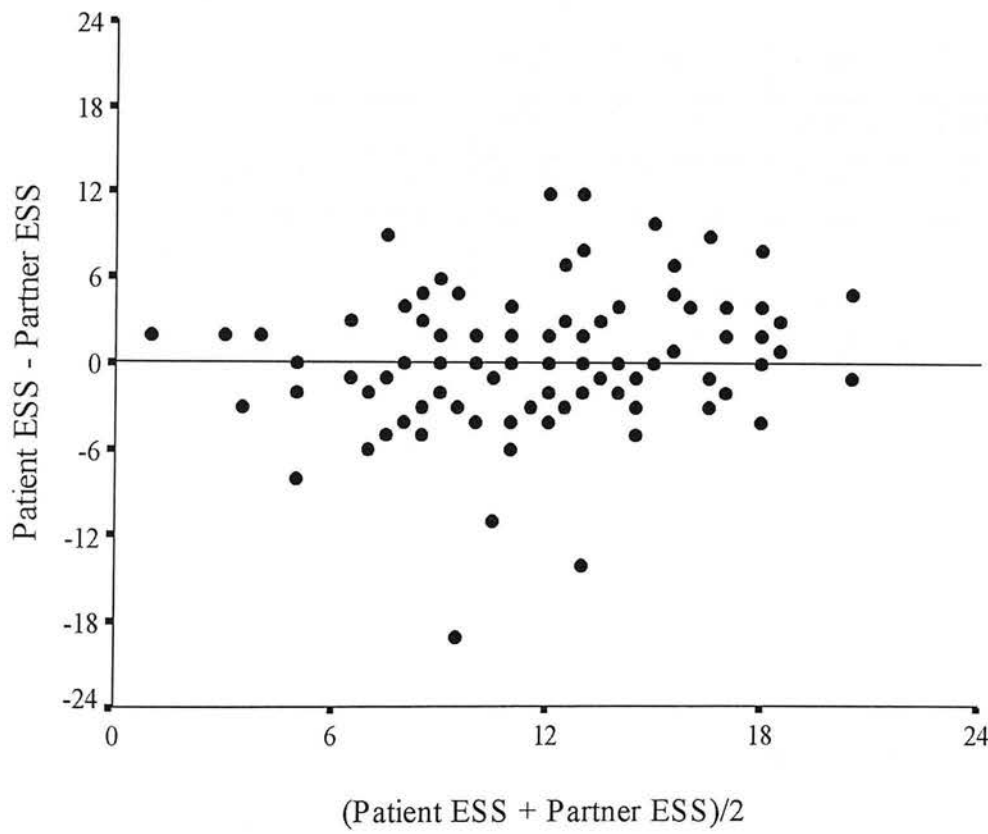
There was no consistent difference in ESS scores between patients and their partners (patient ESS(SD) 12(5), partner ESS 12(4); $p=0.8$). The correlational relationship between patient and partner ESS scores is shown in Figure 4.2.

Figure 4.2; A scatterplot of patient versus partner ESS scores ($r=0.56$, $p<0.0001$); (----- line of identity)



Individual discrepancies between patients and their partners are more clearly demonstrated when this data is represented graphically using a Bland and Altman plot (Figure 4.3). Only 10 of the 103 couples show 100% agreement in their ESS scores. At the other extreme, 13 couples differ by more than 6 points on their ESS score. This graph also demonstrates that there is no tendency for discrepancies between couples to vary with ESS score severity. For example, those patients who score highly on the ESS are not more likely to have a greater discrepancy than those with non-sleepy ESS scores.

Figure 4.3; Bland and Altman plot of relationships between patient and partner ESS scores



A subanalysis was performed on the group of patients (n=66) whose polysomnography found an $\text{AHI} \geq 15$, comparing patient and partner ESS scores. As with the whole population, there was no consistent difference in ESS scores (patient ESS 12(5), partner ESS 11(4); $p=0.1$).

4.3.3 Relationships between ESS scores and nocturnal SAHS variables

There were no significant relationships between the nocturnal SAHS measures and patient or partner ESS scores in the whole sample (Table 4.2; Figures 4.4-4.7). In fact, the relationships were very weak.

Table 4.2; Spearman rank correlation matrix of relationships between nocturnal SAHS measures and patient and partner ESS scores.

	Patient ESS	Partner ESS	Max ESS	Min ESS
Whole sample (n=103)				
AHI	0.02	-0.07	-0.13	0.10
Arousal frequency	-0.01	-0.05	-0.06	0.03
Minimum saturation	0.09	-0.01	0.09	-0.00
AHI≥15 (n=66)				
AHI	0.14	0.27**	0.11	0.32**
Arousal frequency	-0.001	0.07	0.04	0.04
Minimum saturation	0.04	-0.14	0.00	-0.09

**p<0.01

In the patient subgroup with an AHI≥15, again patient ESS did not correlate significantly with nocturnal SAHS variables. Partner ESS and the minimum ESS score of each couple correlated weakly, but significantly, with AHI (Table 4.2), but explained less than 11% of the residual variance.

Figure 4.4; Scatterplot of the relationship between AHI and patient Epworth score (n=103; $\rho=0.02$, p=0.84)

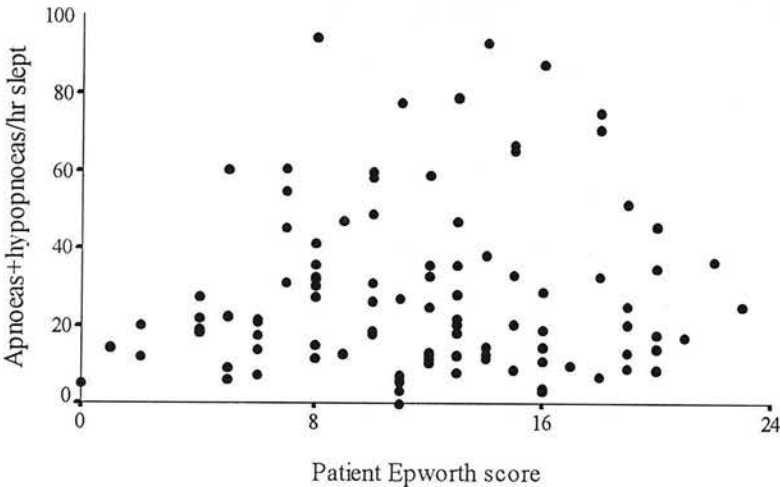


Figure 4.5; Scatterplot of the relationship between AHI and partner Epworth score (n=103; $\rho=-0.07$, p=0.49)

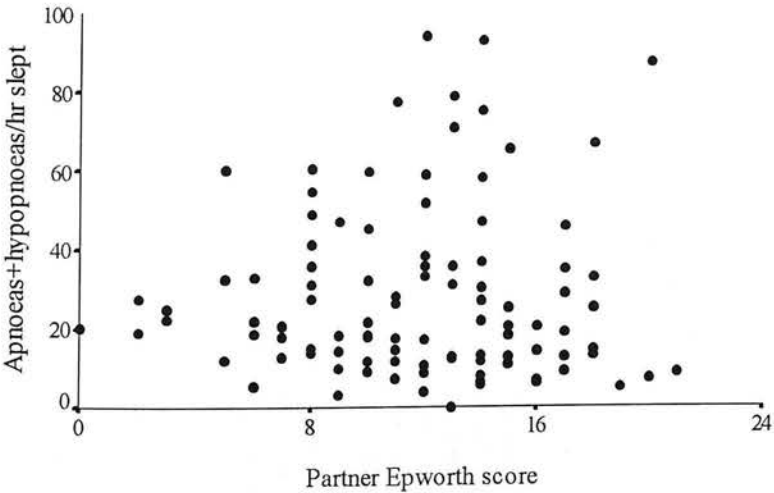


Figure 4.6; Scatterplot of the relationship between arousals and patient Epworth score (n=103; $\rho=-0.01$, $p=0.98$)

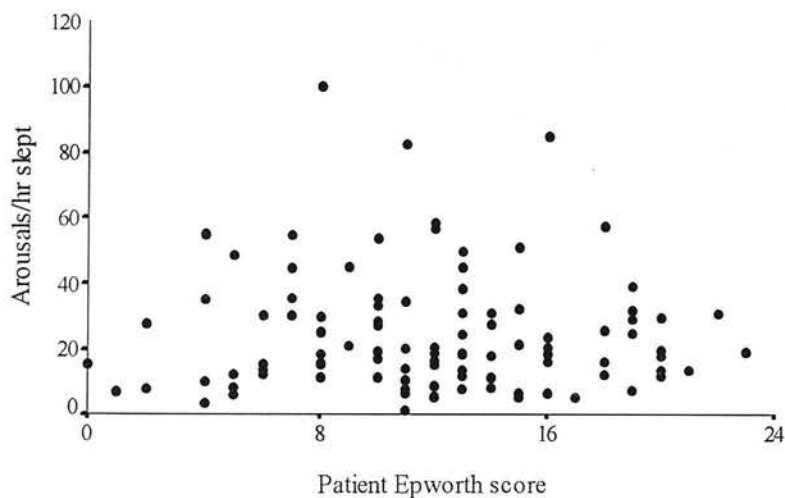
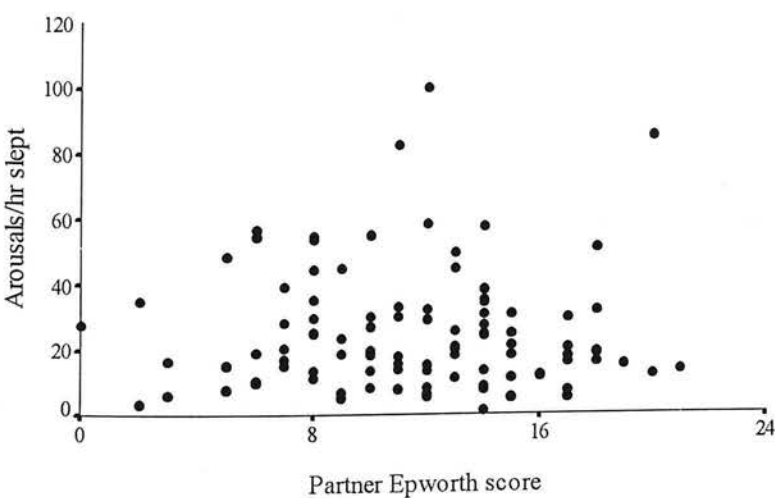


Figure 4.7; Scatterplot of the relationship between arousals and partner Epworth score (n=103; $\rho=-0.05$, $p=0.53$)



4.4 Discussion

Results found that the patient and partner ESS scores were moderately correlated ($r=0.56$, $p<0.0001$). This correlation is congruent with a study by Johns (1994) published during the current investigation, where a significant correlation was found between 50 sets of patients and their partner ESS scores ($\rho=0.74$, $p<0.001$). The current study also demonstrated that the patient and partner ESS scores are not significantly different in either the population as a whole, or in the subgroup with an $AHI\geq 15$. However, Johns (1994) found a small difference in patient and partner ESS scores when using the Wilcoxon t-test (patient ESS(SD) 13(5), partner ESS 14(5); $p=0.04$).

The results of the current study indicate that the patient or their partner can equally assess the patient's sleepiness. Examining individual couple differences (Figure 4.3), most couples will openly discuss the patient's sleepiness and so are likely to show similar scores on the ESS. However, in a few cases, there are large discrepancies between patient and partner scores (Figure 4.3) and such differences are discussed in Section 4.4.1.

The current study improves on Johns' study (1994) by examining possible relationships between patient and partner ESS scores and nocturnal SAHS variables. This study found that in the whole population ($n=103$) presenting at the sleep clinic, there were no significant correlations between ESS variables and nocturnal SAHS variables. This was for both patient and partner ratings of sleepiness. In the subgroup of SAHS diagnosed patients ($AHI\geq 15$), the patient's ESS rating was not significantly related to AHI. This contrasts with an earlier study (Johns 1993) where significant correlations ($r=0.4$, $p<0.001$) were found between the SAHS patient's ESS score and the RDI. Partner ESS and MinESS did significantly relate to AHI, but as such, these relationships are highly dubious clinically as one cannot predict who will have an

AHI \geq 15 at this stage. These results do not therefore answer the question of whether the patient or partner scores are more reliable assessors of daytime sleepiness.

There are two possible reasons for the lack of correlational relationships between nocturnal SAHS variables and ESS scores. The first is that the ESS reflects problems with subjective ratings. The second is that the polysomnography is not measuring variables that predict daytime sleepiness.

4.4.1 Problems with subjective ratings

Individuals have different perceptions of the severity of their sleepiness, making cross-subject comparisons difficult. The variability in ESS scores is reflected in the individual patient and partner differences (Figure 4.3). There are many possible reasons for this variability. Some patients will maximise their symptoms, whilst others will minimise their symptoms, but one cannot prospectively predict which group a patient might belong to. Patients often have no insight into the severity of their sleepiness. Many patients have felt sleepy for so many years that they lose their frame of reference, and it is not until they are established on treatment that they realise how sleepy they were in the untreated state. This has been documented by Engleman et al (1997b), where patients on CPAP scored their untreated sleepiness as significantly higher than their previous baseline estimation. Similarly, patients may not admit to having problems whilst driving, as they feel this may jeopardise their job. Also some patients may not drive very often, or at all, and thus find it hard to imagine themselves in that situation.

There are also difficulties with partners completing the ESS. Partners are not always present in the 8 ESS situations, and so may provide false estimates of sleepiness. For example, with the item 'falling asleep whilst stopped at traffic lights', if the partner is present in the car, the patient driver may be more likely to stay awake due to the presence of a passenger, rather than when driving alone. Patient's complaints about sleepiness may also influence partner's scoring, with some patients discussing their sleepiness and others not.

General causes of variability also exist in the ESS items due to not following the ESS instructions carefully. To try and overcome different lifestyles, the ESS states that if an individual has not been in one of the situations recently, they have to “try and work out” how the situation would affect them. If a patient does not regularly participate in one of the daily items, they may score zero, rather than imagining themselves in that situation. For example, ‘lying down to rest in the afternoon when circumstances permit’. Some patients may have very demanding jobs, and so never lie down in the afternoon, and score zero, rather than imagining what would actually happen if the situation did arise. Individuals may misinterpret their tiredness as sleepiness and so overrate their scores despite being asked to differentiate between these two feelings in the questionnaire. Item 8 (In a car, when stopped for a few minutes in the traffic) may be misinterpreted by some individuals. There is confusion as to whether this question is in the context of being a driver or a passenger.

There are many reasons for ESS scores to vary, and one cannot predict who is going to over or underestimate their sleepiness for any of the above reasons. One can argue that the patient score is more important, as it is their symptoms that require treatment. However, if patients are unaware of their sleepiness, the partner may be the more reliable assessor, yet they are not always present in all ESS situations. Therefore the information from both the patient and partner ESS assessments may provide the best all-round estimate of sleepiness.

4.4.2 Lack of relationships with polysomnography

The lack of significant relationships between ESS scores and polysomnography measures could also be due to polysomnography not providing useful measures of SAHS disease severity. Some correlational studies have found significant relationships between SAHS polysomnographic variables and measures of daytime sleepiness (Roehrs et al 1989, Johns 1991, Poceta et al 1992), whereas other studies have not (Dement et al 1978, Cheshire et al 1992). Therefore further work on the relationships between nocturnal SAHS measures and daytime sleepiness is required (Chapter 5) to

determine whether the most appropriate measures of SAHS severity and daytime function are being used.

4.4.3 Conclusion

This study suggests that both the patient and partner ESS scores should be used to provide information about the patient's sleepiness. If there are large discrepancies between the two ESS scores, then this should be discussed with the couple in the clinic to determine the cause of this discrepancy.

The lack of relationships between the ESS and nocturnal SAHS measures presented here can lead to two possible conclusions. The first is that the ESS is a measure of sleepiness open to great variability in interpretation by both the patient and the partner, and that it is better to perform nocturnal polysomnography and measures of objective daytime sleepiness whenever possible. Alternatively, the scores given by the patient and their partner may accurately represent the level of sleepiness suffered by the patient, and regardless of the AHI or arousal frequency laboratory based evidence, it is the ESS measure, the degree of daytime sleepiness, that is important and should determine who receives CPAP therapy. One study (Maycock 1996) surveyed self-reported driving problems and ESS sleepiness and found the ESS score to significantly relate to the frequency of reported road accidents and tendency to doze at the wheel. Self-reported outcomes such as these play an important role in public health safety.

It is most likely that the role of the ESS lies somewhere in the middle. As mentioned by Johns (1991), a high ESS score by itself is not diagnostic. The ESS score alone cannot be used to determine the mode of investigation or the likelihood of an individual having SAHS. The ESS does provide helpful information when used in conjunction with other questions (Appendix B) and discussion at the initial clinic consultation. It is all this information together which has clinical predictive value and not the ESS alone. This predictive information can then allow limited sleep studies to sometimes be performed rather than full polysomnography and allows labour intensive

MSLTs and MWTs to only be used for special cases in SAHS and not as routine measurements.

The main aim of this thesis, to determine factors affecting daytime function, will include a further correlational analysis of the ESS and nocturnal SAHS measures in a larger sample (Chapter 5). In this protocol, the MSLT and the MWT are used along with the ESS and this study will determine if the ESS relates to these objective measures of daytime sleepiness (Chapter 6). Also Chapter 7 examines the use of the ESS in CPAP therapy follow-up and determines how the ESS and other baseline SAHS measures relate to CPAP use.

Chapter 5

Nocturnal Correlates of Daytime Function in SAHS Patients

5.1 Introduction

As discussed in Chapter 2, patients with the sleep apnoea/hypopnoea syndrome suffer from excessive daytime sleepiness (Roth et al 1980, Whyte et al 1989), cognitive decrements (Greenberg et al 1987, Cheshire et al 1992), and decreased psychological well-being (Smith & Shneerson 1995). Previous correlational studies have examined the possible causative relationships between nocturnal features of SAHS and daytime function (Roth et al 1980, Yesavage et al 1985, Guilleminault et al 1988b, Roehrs et al 1989, Millman et al 1989, Bedard et al 1991b, Poceta et al 1992, Cheshire et al 1992, Chervin et al 1995, Smith & Shneerson 1995, Kim et al 1997). Despite the number of correlational studies, there is still controversy as to whether daytime sleepiness in SAHS is primarily due to sleep fragmentation (Roehrs et al 1989, Poceta et al 1992), to repetitive nocturnal hypoxaemia (Bedard et al 1991b), both or neither (Cheshire et al 1992, Chervin et al 1995). Studies examining relationships between nocturnal SAHS variables and cognitive function tests also found varying results. Significant relationships with cognitive decrements have been related to both hypoxaemia (Greenberg et al 1987, Bedard et al 1991b, Cheshire et al 1992) and sleep fragmentation (Cheshire et al 1992). Relationships have also been found between nocturnal hypoxaemia and psychological decrements (Millman et al 1989, Smith & Shneerson 1995).

The reasons for performing a further correlational study are based on the poor methodology of some of the previous studies. The nocturnal SAHS features of respiratory events, arousals and oxygen desaturations are interrelated, due to the repetitive cyclical nature of the syndrome (see Figure 1.1), yet previous studies have often focused on the causative role of just one or two of the major nocturnal SAHS variables. For example, Bedard et al (1991b) found significant correlations between minimum oxygen saturation and sleepiness and performance, and between %

awakenings and performance (all $r > 0.5$, $p < 0.05$). The number of awakenings is a crude measure of sleep fragmentation and had microarousal frequency been measured, perhaps significant relationships with sleepiness would have been found, and that hypoxaemia may actually covary with arousal frequency. Other studies have also limited the number of major nocturnal variables used in correlational analysis, often omitting some important measures. Studies have not measured AHI (Smith & Shneerson 1995), hypopnoeas (Roth et al 1980, Bedard et al 1991b), microarousals (Yesavage et al 1985, Chervin et al 1995, Smith & Shneerson 1995, Kim et al 1997), or hypoxaemia (Yesavage et al 1985, Kim et al 1997). It is therefore possible that significant relationships reported in the above studies are not the only important ones. Other unmeasured nocturnal variables could contribute to the causal variance. Unless nocturnal SAHS variables are experimentally isolated, as discussed in section 2.7, it is important to examine the contributing role of all the routinely measured nocturnal SAHS variables. This was done in the current study.

Previous studies have also used older definitions of arousal (Roth et al 1980, Guilleminault et al 1988b, Roehrs et al 1989, Bedard et al 1991b). For example, studies have measured the number of 15 second (R & K) awakenings (Guilleminault et al 1988b, Bedard et al 1991b, Chervin et al 1995), rather than microarousals. Such microarousals affect daytime function in experimental sleep fragmentation studies (Philip et al 1994, Roehrs et al 1994, Martin et al 1996) and occur frequently in SAHS (Martin et al 1997c). Therefore in the current study, microarousals were measured.

Many studies have focused on single areas of daytime function such as daytime sleepiness (Roehrs et al 1989, Poceta et al 1992, Johns 1993, Chervin et al 1995), cognitive performance (Yesavage et al 1985, Kim et al 1997), and psychopathology (Millman et al 1989, Smith & Shneerson 1995). In keeping with the previous correlational study from Edinburgh (Cheshire et al 1992), the current study aims to include a broad range of daytime function tests. In addition to those measures used by Cheshire et al (1992), more recent tests have been incorporated, such as the

maintenance of wakefulness test (MWT) (Poceta et al 1992) and the short form (SF) 36 questionnaire (Ware & Sherbourne 1992).

Large patient populations are also required to perform convincing correlational studies. Previous case-control studies have used relatively small numbers of patients (Roth et al 1980, n=10 SAHS patients; Stepanski et al 1984, n=15 SAHS patients), and the correlational analysis has followed. Other small sample correlational studies have also been performed *a priori* (Bedard et al 1991b, n=20 SAHS patients; Cheshire et al 1992, n=29 SAHS patients, Chervin et al 1995, n=28 SAHS patients). Conversely, large scale correlational studies by Roehrs et al (1989) and Poceta et al (1992) used 466 and 322 SAHS patients, respectively. In the current study, I aimed to study a large number of patients, limited by the time constraints of the project, and availability of suitable patient referrals.

The patient samples previously studied have also varied in their recruitment criteria. A homogenous sample of patients may mask potential correlations by attenuating the variance. For example, Roth et al (1980) and Bedard et al (1991b) studied patients with moderate to severe disease only, and so may have reduced the ability to detect potential correlations. In the current study it was planned to recruit an unselected, consecutive, heterogeneous patient sample with a wide range of disease severity.

The major hypothesis of this investigation was that brief microarousals from sleep cause the sleepiness and impaired daytime function found in SAHS. The current study compares overnight polysomnography with daytime measures of objective sleepiness, cognitive performance and psychopathology, in a large, unselected, consecutive patient sample. By examining the possible predictors of daytime dysfunction, this study aims to identify which nocturnal features affect daytime function, and therefore predict who requires CPAP treatment.

5.2 Methods

5.2.1 Patient recruitment

Participants in the study were an unselected consecutive sample of clinical patients suspected of having SAHS, who were referred to the Edinburgh sleep centre by general practitioners and hospital specialists. Prior to the initial outpatient consultation, all patients and their partners completed an in-house sleep/wake questionnaire (Appendix B). The information from the questionnaire, in addition to the clinical interview and the referral letter, determined that patients who gave a convincing history suspicious of SAHS underwent diagnostic overnight polysomnography.

Some patients were excluded from the study prior to their polysomnography, as they did not fulfil the recruitment criteria (Table 5.1). For inclusion, patients had to be between 18 and 75 years old and live within 50 miles of the Edinburgh sleep centre. This distance restriction was to ensure that patients did not have to arise exceptionally early on their daytime test day in order to arrive at the sleep centre for 9:00 am and possibly influence daytime sleepiness results. From casenote and sleep questionnaire evaluation, patients were also excluded who had evidence of coexisting causes of daytime sleepiness, such as night or rotating shift workers, or patients who regularly self-reported a sleep duration of less than 5 hours per night. Patients who described symptoms highly suspicious of other sleep disorders were also excluded at this stage. Patients with major psychiatric and neurological disorders and coexisting causes of hypoxaemia were also excluded (e.g. COPD, nocturnal asthma; Table 5.1).

On the morning after overnight polysomnography, consecutive patients who had not given a prior history of the above exclusion criteria (Table 5.1) were approached by a sleep physician and then by myself to ask if they would participate in the study and return for daytime tests. Overnight records were then scored to confirm an absence of periodic limb movement disorder (PLMD) and an $AHI \geq 5$, for the patients to remain in the study and return for daytime testing.

Table 5.1; Patient recruitment criteria

Inclusion Criteria

- Self-reported symptoms of either sleepiness ($ESS \geq 8$) or 2 other major symptoms of SAHS
- Aged 18-75
- Living within 50 miles of the sleep centre
- $AHI \geq 5$

Exclusion Criteria

- Coexisting causes of daytime sleepiness
- Self-reported average sleep duration of < 5 hours per night
- Coexisting sleep disorders
- Major psychiatric and neurological disorders
- Coexisting causes of hypoxaemia

167 patients were eligible for the study and 150 (136 men; Table 5.2) agreed to participate. Fifteen declined because of work pressures ($n=14$) and family commitments ($n=1$), and two patients were further excluded from the study due to having a poor night's sleep (< 6 hours, subjective rating of total sleep time) prior to daytime testing.

Table 5.2; Patient population data (n=150)

Measurement	mean (SD)	range
Age (years)	50 (10)	22 - 71
BMI (kg/m ²)	32 (7)	20 - 64
AHI (per hr slept)	45 (31)	7 - 144
Arousal frequency (per hour slept)	51 (28)	8 - 141
Minimum oxygen saturation (%)	83 (11)	34 - 95
% Wake*	22 (12)	2 - 61
% Stage 1 sleep*	8 (7)	0.3 - 35
% Stage 2 sleep*	44 (11)	15 - 72
% Slow wave sleep*	11 (7)	0 - 38
% REM sleep*	15 (6)	1.6 - 30
Epworth sleepiness scale (mean)	12 (5)	0 - 24
MSLT - mean SOL (mins)	9.7 (4.7)	2.5 - 20
MWT - mean SOL (mins)	27 (12)	2.6 - 40

BMI=Body mass index; AHI=Apnoea+hypopnoea index; REM=Rapid eye movement; MSLT=multiple sleep latency test; MWT=maintenance of wakefulness test; SOL=sleep onset latency; * Values for sleep stages are expressed as a percentage of sleep period time.

The study patients all had self-reported symptoms of either sleepiness or two other major symptoms of SAHS (Whyte et al 1989), listed in Table 5.3. Sleepiness was defined as an ESS \geq 8, as used in previous studies from this sleep centre (Engleman et al 1994a, 1997a). The symptom ratings were taken from in-house symptom and sleep/wake questionnaires (Appendices A & B). The percentages of SAHS symptoms reported by patients are documented in Table 5.3.

Table 5.3; Percentages of self-reported patient symptoms

Self-reported symptoms*	% patients reporting symptom
Snoring	100
Unrefreshing sleep	77
Daytime sleepiness (ESS≥8)	75
Witnessed breathing pauses	49
Choking episodes	33
Sleepiness whilst driving	21
Nocturia	9

ESS=Epworth sleepiness scale; *All symptoms reported from in-house symptom and sleep/wake questionnaires (Appendices A & B).

5.2.2 Nocturnal Measurements

Full nocturnal polysomnography (PSG) and subsequent off line data analysis were performed as outlined in Chapter 3. New off line measures of sleep quality were also used in addition to the routine PSG measures. The frequency of sleep stage shifts to an R & K defined wake page was recorded per hour of sleep (stage shifts to wake index; SSWI). Sleep continuity was also measured by identifying the longest period of uninterrupted sleep using an in-house computer program. This program marked the longest run of sleep epochs terminating in a wake epoch, in addition to the longest uninterrupted period for each sleep stage in turn. The same procedure was also used to find the median length of continuous sleep for all sleep stages together, and for each individual sleep stage.

The total numbers of arousals, stage shifts to wake, respiratory events and 2,3, and 4% desaturations were all divided by total sleep time (TST) to give frequencies per hour slept.

5.2.3 Daytime Assessments

Daytime assessments were chosen to measure a wide range of functional areas thought to be affected by SAHS (Cheshire et al 1992, Engleman et al 1994a) (Table 5.4). All assessments are described in Chapter 3, and were performed and scored according to standard recommendations. All patients underwent an identical test battery (Table 5.5), performed at the same time of day in all subjects. Tests were undertaken after a normal night's sleep at home within one month of the overnight polysomnography.

Body mass index, collar and waist circumferences were recorded on the morning of the test day. A background questionnaire was completed by myself, asking the patient about their medication, medical history, tobacco and alcohol consumption, occupation and educational history.

Objective sleepiness was measured using both the MSLT and MWT following the protocol described in section 3.4.2. The sleep onset latency (SOL) was determined from 'lights out' until the first 30 second epoch of any sleep stage (Thorpy 1992).

The questionnaires (Table 5.5) were given to each patient in the morning after the 10:00 MSLT. Each patient was guided through the questionnaires and then left alone for 20 minutes to complete them, with any queries answered at the end.

Cognitive function tests were explained by myself, following the standard instructions given for each test. Patients were instructed to withdraw from caffeine on the evening prior to the daytime testing, and throughout the test day decaffeinated drinks were provided.

Table 5.4; Daytime function measures

<u>Questionnaires</u>	
Self reported sleepiness	-Stanford sleepiness scale -Epworth sleepiness scale
Self reported SAHS symptoms	-in house symptom questionnaire
Well-being and quality of life	-Hospital anxiety and depression (HAD) scale -Nottingham health profile (NHP) part 2 Short Form (SF)36
Personality	-Eysenck personality questionnaire revised (EPQ-R)
<u>Cognitive performance measures</u>	
Premorbid intelligence	-National adult reading test (NART)
General cognitive function	-Digit symbol -Block design -Trail making A & B
Attention & concentration	-Paced auditory serial addition task (PASAT) -Steer Clear
Information Processing Time	-Simple unprepared reaction time task (SURT)

Table 5.5; Daytime function testing schedule

09:00	Wire up patient, anthropometry, background information questionnaire <i>(minimum 20 minutes free time)</i>
10:00	MSLT Questionnaires <i>(minimum 20 minutes free time)</i>
11:00	MWT <i>(minimum 20 minutes free time)</i>
12:00	MSLT Lunch <i>(minimum 40 minutes free time)</i>
13:00	MWT Reaction time task <i>(minimum 10 minutes free time)</i>
14:00	MSLT Cognitive function battery <i>(minimum 10 minutes free time)</i>
15:00	MWT <i>(minimum 20 minutes free time)</i>
16:00	MSLT Steer Clear for 30 minutes <i>(minimum 10 minutes free time)</i>
17:00	MWT

5.2.4 Statistical Analysis

The majority of variables were non-normally distributed. Therefore non-parametric statistics were used throughout for consistency. The relationships between nocturnal SAHS variables and daytime function measures were evaluated by Spearman rank correlations. Both age and awake oxygen saturation correlated significantly with a number of daytime variables, therefore all correlations were partial, controlling for age and awake oxygen saturation. Multiple regression analysis on ranked variables was used to identify independent predictors when an outcome measure significantly correlated with more than one variable. As age (Lezak 1983) and awake oxygen saturation (Grant et al 1982) affect daytime function, they were entered into the multiple regression analysis prior to stepwise regression of the significant correlates. All tests were 2-tailed and a probability value of less than 0.05 was accepted as statistically significant. All data were analysed using SPSS for Windows 6.1. The statistically significant results in this chapter are represented in the tables in bold type for clarity.

5.3 Results

5.3.1 Relationships with measures of daytime sleepiness

Sleep quality

The arousal frequency did not correlate significantly with either subjective or objective measures of daytime sleepiness (Figures 5.1, 5.2, 5.3; Table 5.6).

Figure 5.1; Scatterplot of the arousal frequency versus mean MSLT ($\rho=0.12$, $p=0.14$)

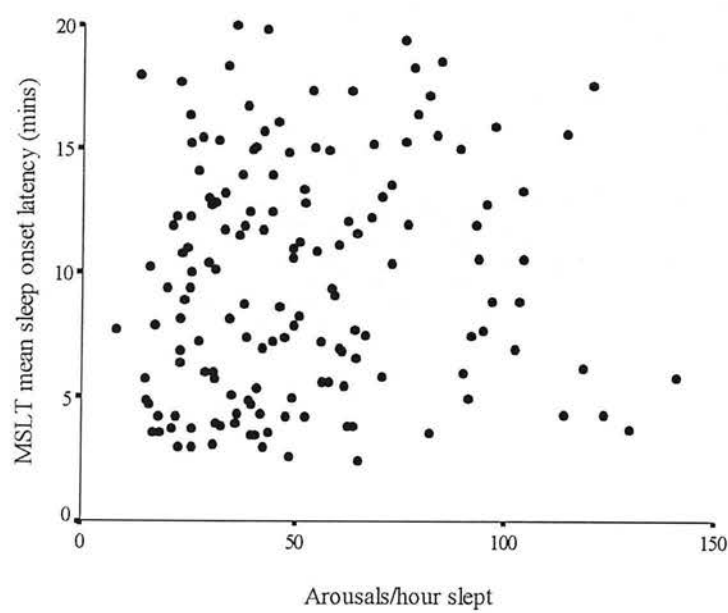


Figure 5.2; Scatterplot of the arousal frequency versus mean MWT ($\rho=0.08$, $p=0.36$)

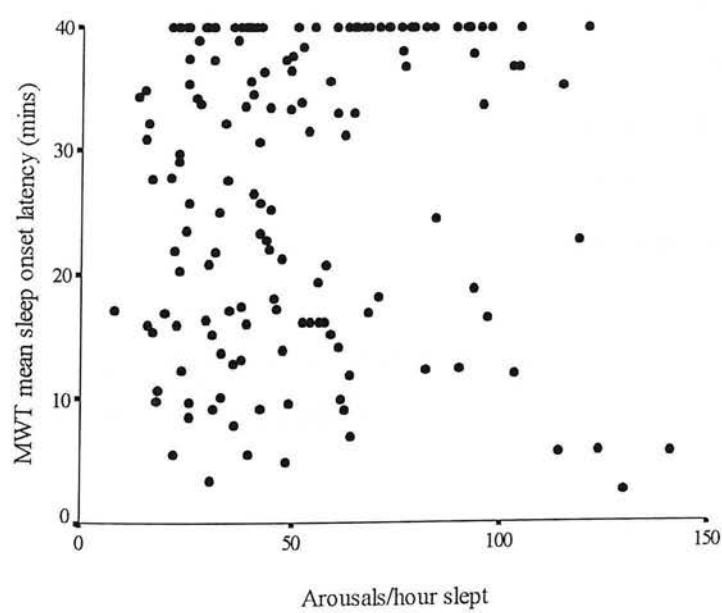
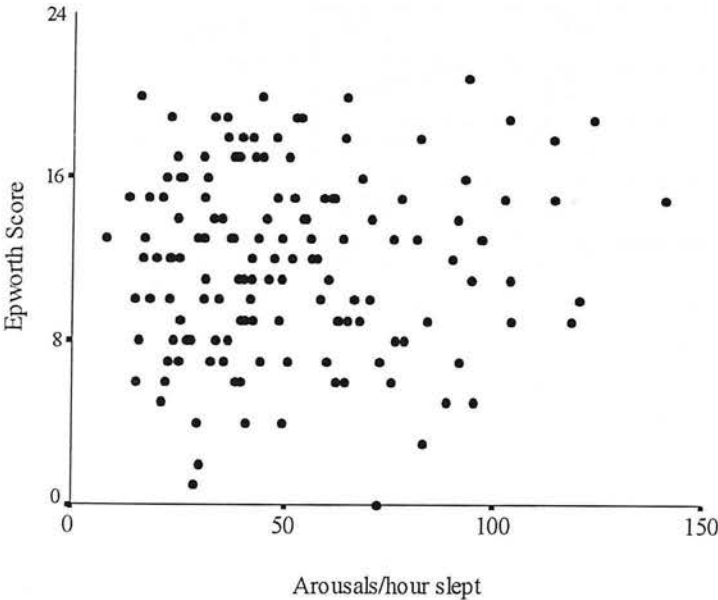


Figure 5.3; Scatterplot of the arousal frequency versus Epworth score ($\rho=0.03$, $p=0.75$)



Percentages of sleep stages and stage shifts to wake demonstrated significant relationships with both the MSLT and MWT in the unexpected direction, i.e. a better nocturnal sleep quality was associated with shorter latencies on the MSLT and MWT (Table 5.6; Figures 5.4-5.7). Paradoxical relationships were also found between measures of sleep continuity and objective sleepiness (Table 5.6; Figures 5.8 & 5.9). For example, a greater median length of uninterrupted sleep was associated with a shorter latency on the MSLT (Figure 5.9). To reduce the number of nocturnal variables, only the median and longest period of all sleep stages together are reported in Table 5.6 rather than continuity data for each individual sleep stage. No significant relationships were found between subjective sleepiness as measured by the ESS and sleep quality variables (Table 5.6).

Table 5.6; Spearman rank correlation matrix of relationships between nocturnal SAHS sleep quality measures and daytime sleepiness. All correlations are controlled for age and awake oxygen saturation

	MSLT	MWT	ESS
Arousal Frequency	0.12	0.08	0.03
% wake	0.31***	0.24**	-0.05
% stage 1 sleep	0.22**	0.16	-0.01
% stage 2 sleep	-0.26**	-0.15	-0.03
% slow wave sleep	-0.16	-0.07	-0.04
% REM sleep	-0.17	-0.15	0.08
TST	-0.38***	-0.20*	0.06
SSWI	0.28**	0.18*	-0.05
longest length of sleep	-0.20*	-0.16*	0.002
median length of sleep	-0.23**	-0.30***	0.06

MSLT=multiple sleep latency test; MWT=maintenance of wakefulness test; ESS=Epworth sleepiness scale; REM=rapid eye movements; TST=total sleep time; SSWI=stage shifts to wake index; *p<0.05, **p<0.01, ***p<0.001

Figure 5.4; Scatterplot of % wake versus mean MSLT ($\rho=0.31$, $p<0.0001$)

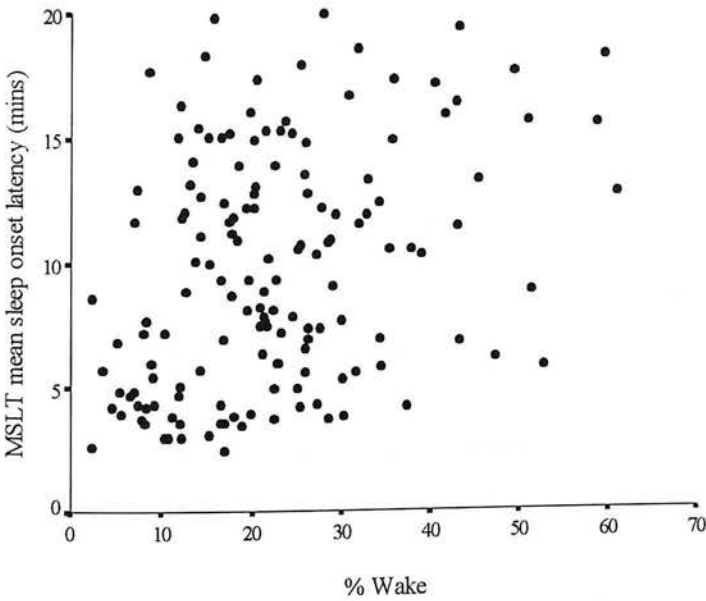


Figure 5.5; Scatterplot of % wake versus mean MWT ($\rho=0.24$, $p=0.004$)

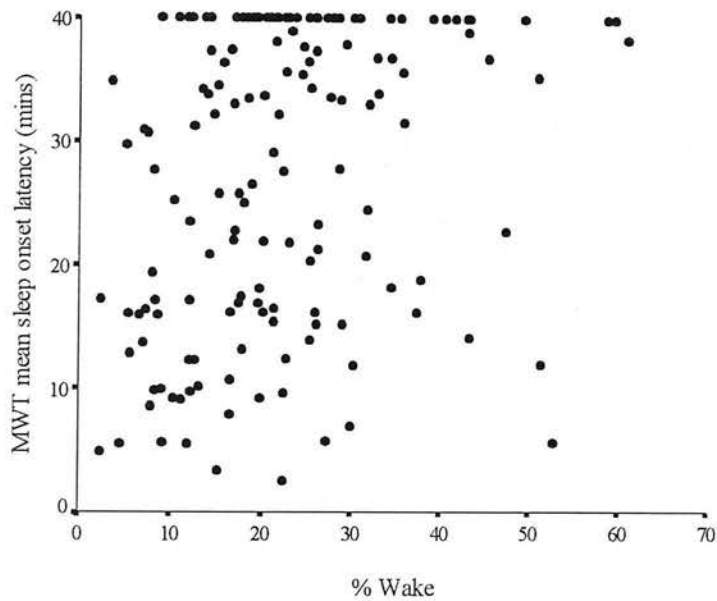


Figure 5.6; Scatterplot of % slow wave sleep versus mean MSLT ($\rho=-0.16$, $p=0.06$)

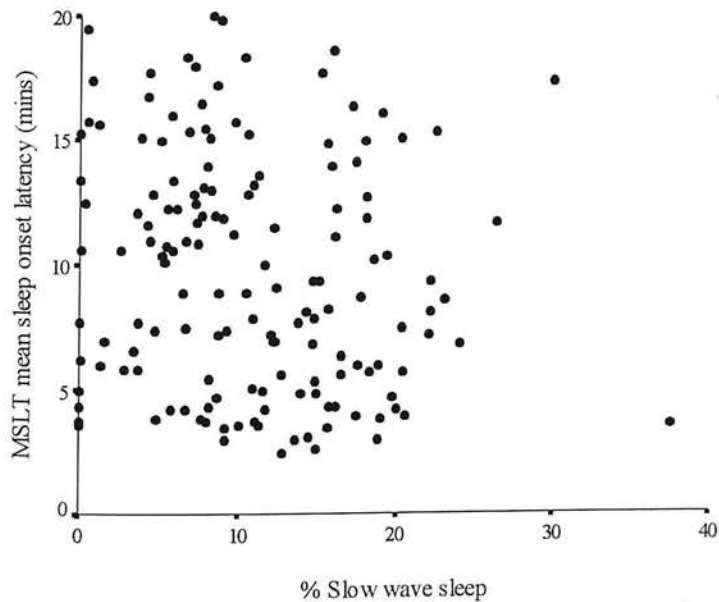


Figure 5.7; Scatterplot of % slow wave sleep versus mean MWT ($\rho=-0.07$, $p=0.38$)

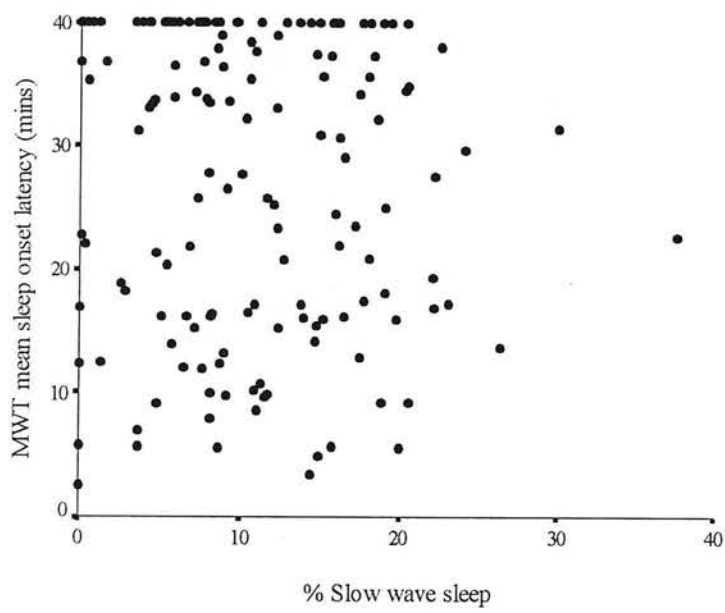


Figure 5.8; Scatterplot of the median length of uninterrupted sleep versus mean MSLT ($\rho=-0.23$, $p=0.005$)

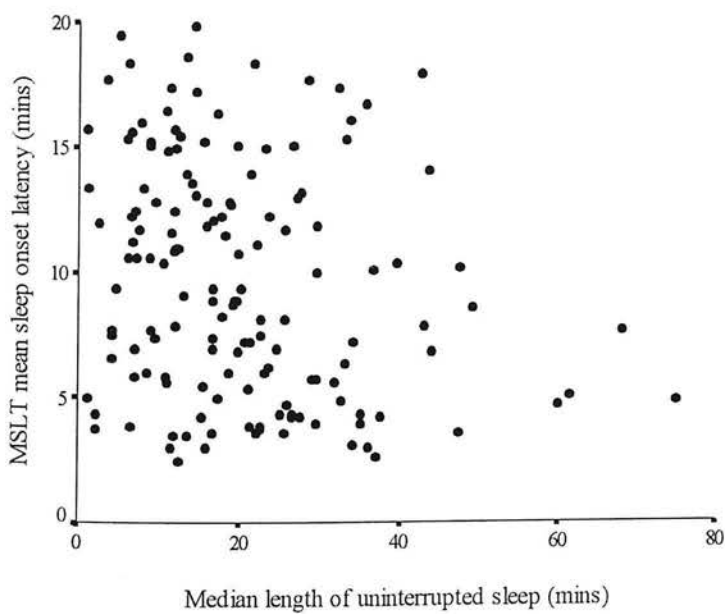
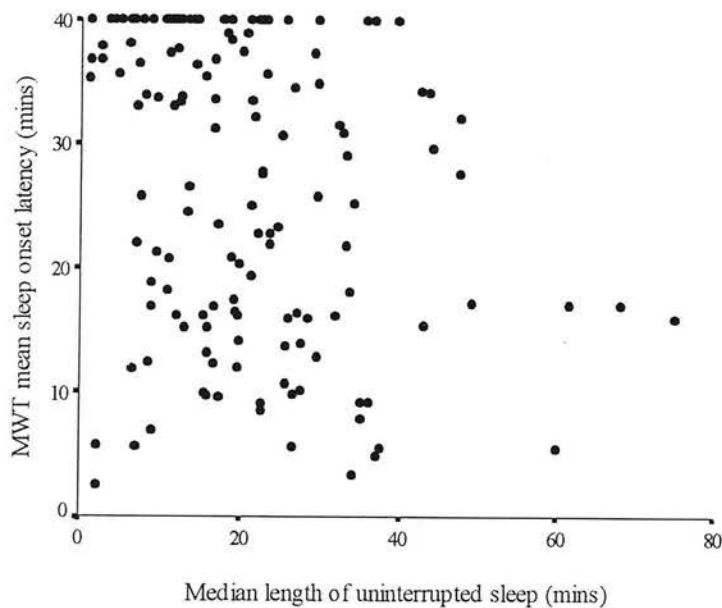


Figure 5.9; Scatterplot of the median length of uninterrupted sleep versus mean MWT ($\rho=-0.30$, $p<0.0001$)



Breathing pattern

AHI did not significantly correlate with objective or subjective measures of daytime sleepiness (Figures 5.10-5.12; Table 5.7).

Figure 5.10; Scatterplot of AHI versus mean MSLT ($\rho=0.02$, $p=0.85$)

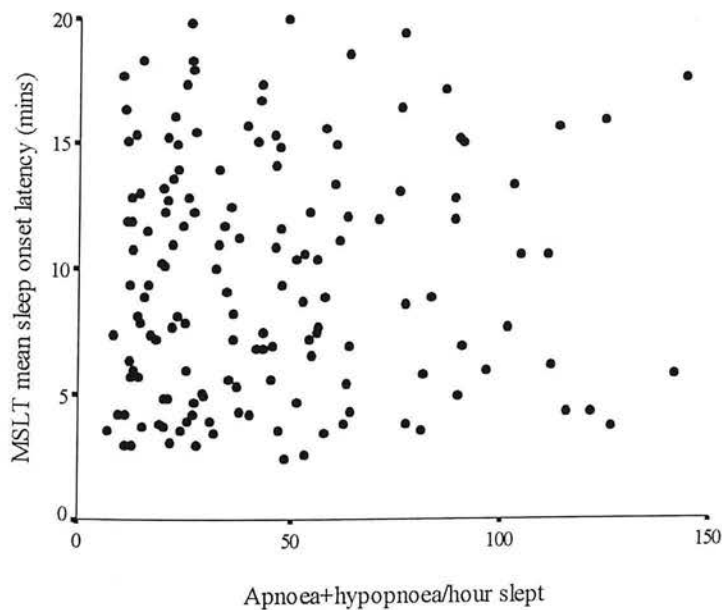


Figure 5.11; Scatterplot of AHI versus mean MWT ($\rho=0.05$, $p=0.55$)

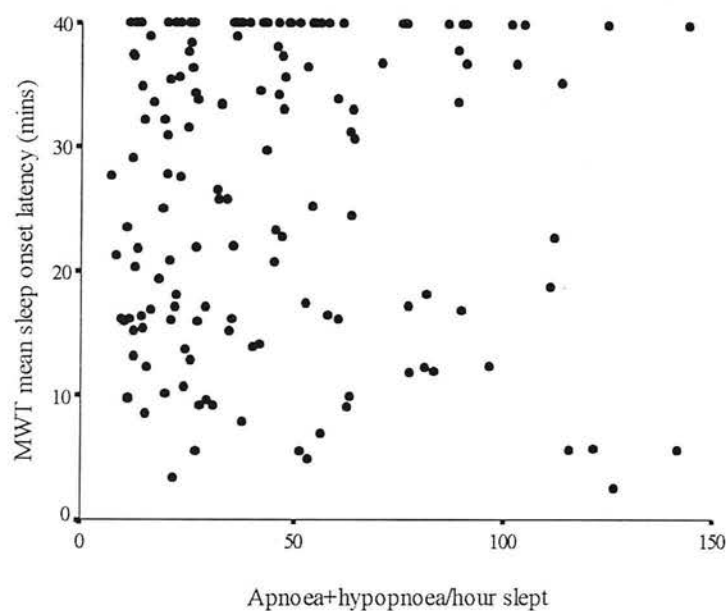


Figure 5.12; Scatterplot of AHI versus Epworth score ($\rho=-0.04$, $p=0.66$)

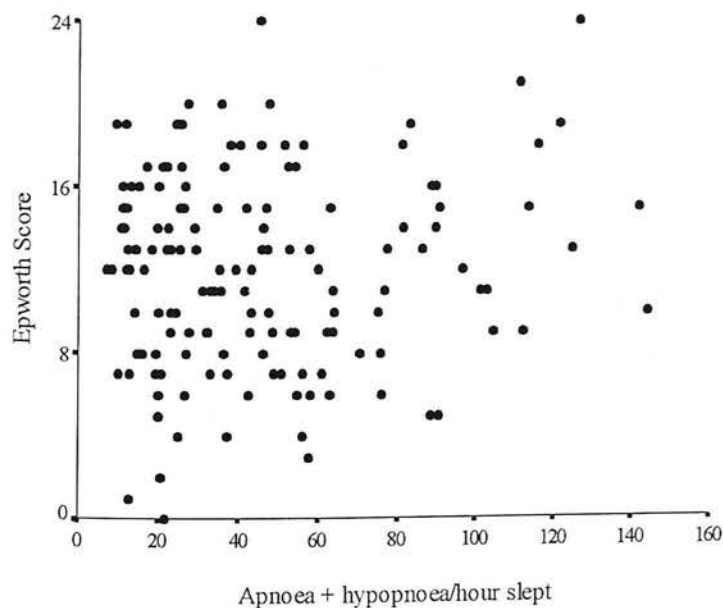


Table 5.7; Spearman rank correlation matrix of relationships between nocturnal SAHS breathing and oxygenation measures and daytime sleepiness. All correlations are controlled for age and awake oxygen saturation

	MSLT	MWT	ESS
AHI	0.02	0.05	-0.04
2% desats	0.12	0.03	0.06
3% desats	0.07	-0.03	0.07
4% desats	0.07	-0.03	0.06
Minimum SaO₂	-0.06	0.19*	-0.22*

MSLT=multiple sleep latency test; MWT=maintenance of wakefulness test; ESS=Epworth sleepiness scale; AHI=apnoea+hypopnoea index; *p<0.05

Oxygenation

Minimum oxygen saturation correlated weakly, but significantly, with MWT (Figure 5.14) and Epworth score (Figure 5.15) in the expected direction (Table 5.7). No other measures of oxygenation significantly correlated with MSLT, MWT or ESS (Table 5.7; Figures 5.13, 5.16-5.18).

Figure 5.13; Scatterplot of % minimum oxygen saturation versus mean MSLT ($\rho=-0.06$, $p=0.45$)

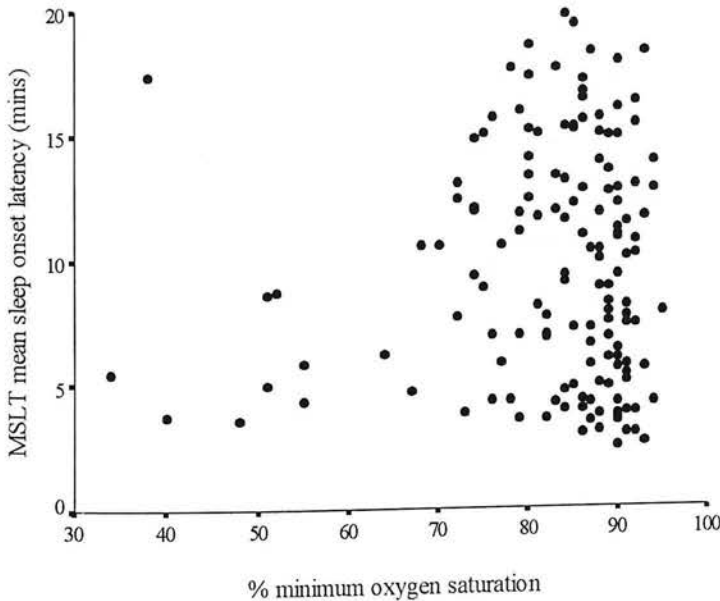


Figure 5.14; Scatterplot of % minimum oxygen saturation versus mean MWT
($\rho=0.19$, $p=0.02$)

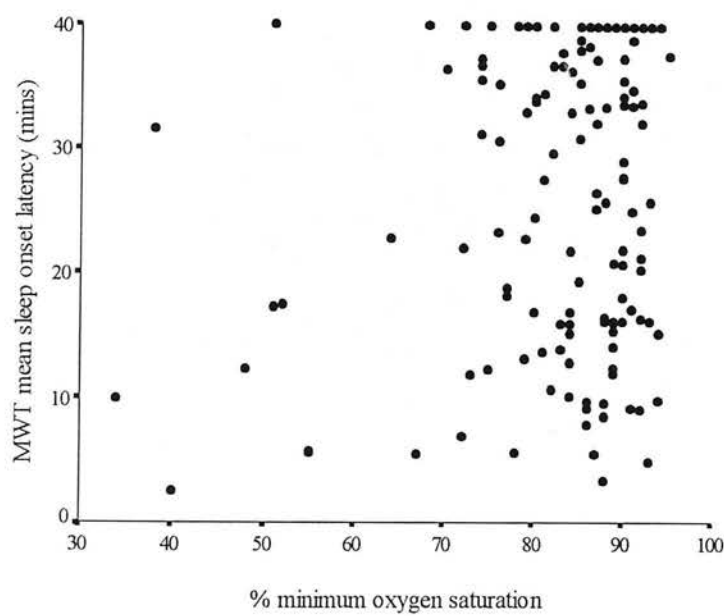


Figure 5.15; Scatterplot of % minimum oxygen saturation versus mean Epworth score
($\rho=-0.22$, $p=0.005$)

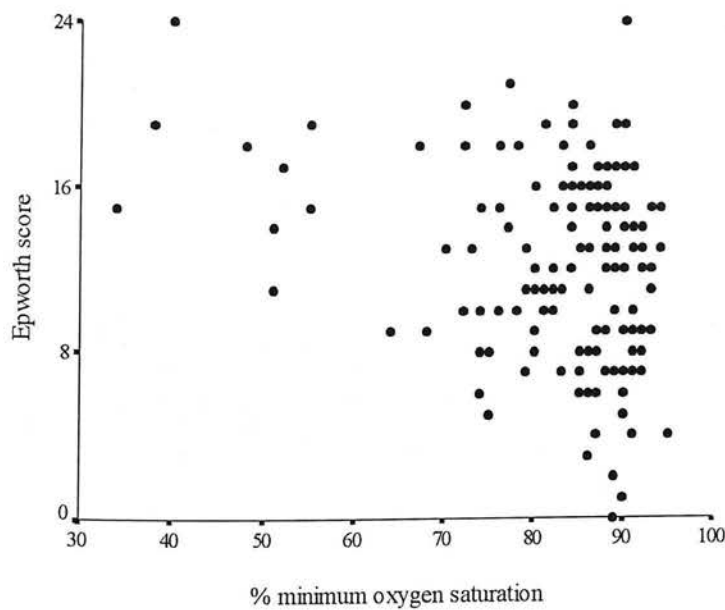


Figure 5.16; Scatterplot of 2% desaturations versus mean MSLT ($\rho=0.12$, $p=0.15$)

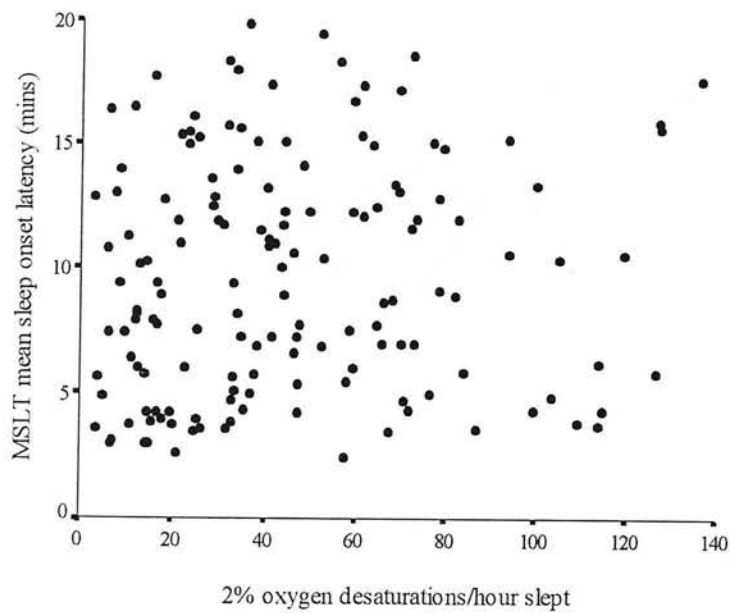


Figure 5.17; Scatterplot of 2% desaturations versus mean MWT ($\rho=0.03$, $p=0.69$)

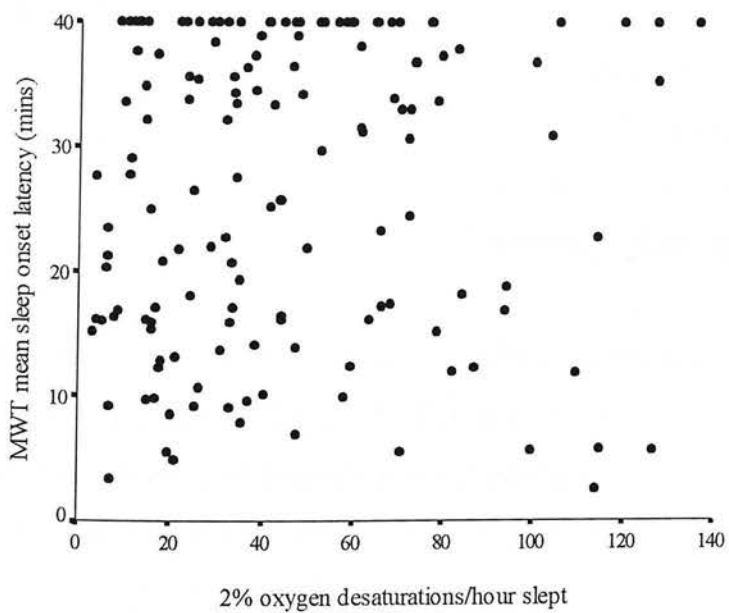
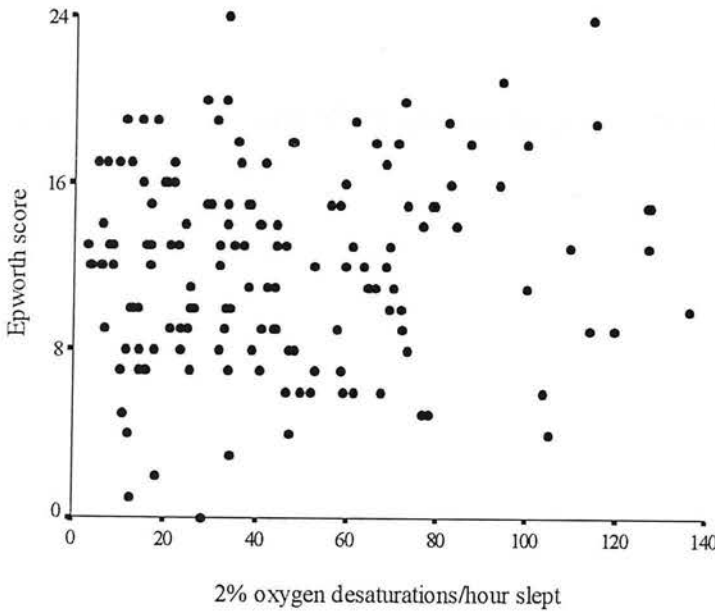


Figure 5.18; Scatterplot of 2% desaturations versus Epworth score ($\rho=0.06$, $p=0.35$)



5.3.2 Relationships with cognitive function measures

Sleep quality

The arousal frequency significantly correlated with reaction time gaps (1 gap = reaction time response >1 sec) i.e. a higher arousal frequency was associated with a greater number of reaction time responses over 1 second. No other cognitive function score significantly related to the arousal frequency (Figure 5.19; Table 5.8).

Percentage stage 1 sleep significantly correlated with digit symbol ($r=-0.19$, $p<0.05$) and PASAT 2 secs ($r=-0.17$, $p<0.05$) in the expected direction, i.e. greater % stage 1 sleep (an indication of sleep fragmentation) was associated with better performance scores. Percentage SWS significantly correlated with reaction time gaps ($r=-0.21$, $p<0.05$), i.e. greater % SWS (an indication of sleep continuity), the better the performance. TST also significantly correlated with digit symbol ($r=0.19$, $p<0.05$),

and SSWI with Steer Clear % hits ($r=-0.19$, $p<0.05$). The median and longest runs of continuous sleep significantly correlated with Steer clear % hits ($r=0.23$, $p<0.01$) and counterintuitively with reaction time gaps ($r=0.19$, $p<0.05$), respectively. All of these significant correlations were weak, each explaining less than 6% of the variance.

Figure 5.19; Scatterplot of the arousal frequency versus the performance IQ score ($\rho=-0.10$, $p=0.23$)

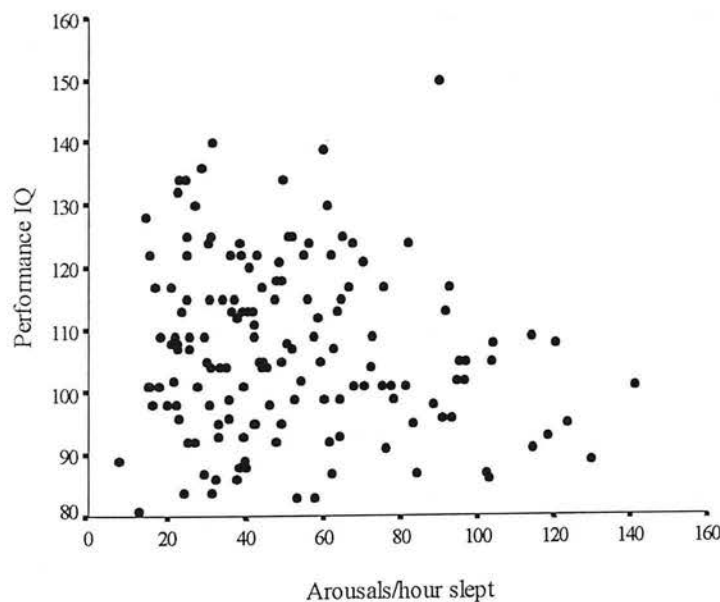


Table 5.8; Spearman rank correlation matrix of relationships between nocturnal SAHS arousal, breathing and oxygenation measures and cognitive function measures. All correlations are controlled for age and awake oxygen saturation

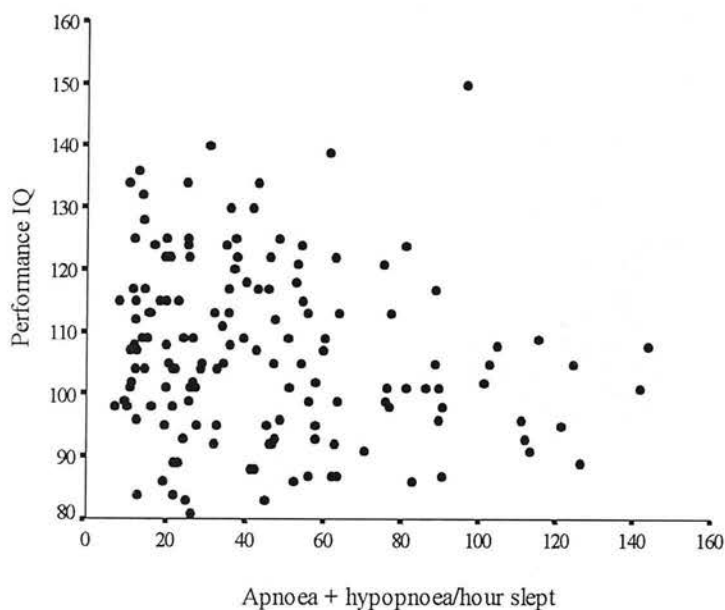
	Arousal	AHI	2% desats	3% desats	4% desats	min sat
Block Design	-0.03	-0.09	-0.13	-0.13	-0.10	0.09
Digit Symbol	-0.07	-0.12	-0.18*	-0.15	-0.12	0.11
Steer Clear % hits	-0.01	0.03	0.08	0.04	0.02	-0.06
IQ decrement	0.06	0.14	0.19*	0.20*	0.18*	-0.18*
PASAT 2 secs	-0.14	-0.14	-0.15	-0.10	-0.09	0.09
PASAT 4 secs	-0.08	-0.12	-0.17*	-0.14	-0.13	0.15
Performance IQ	-0.10	-0.17*	-0.23**	-0.22**	-0.19*	0.19*
SURT false	-0.03	-0.03	-0.03	-0.03	-0.07	0.02
SURT gaps	0.19*	0.12	0.13	0.14	0.12	-0.17*
SURT mean	-0.07	-0.10	0.03	-0.03	-0.03	-0.02
Trail making A	0.07	0.02	0.06	0.07	0.06	0.04
Trail making B	0.07	0.06	0.13	0.15	0.16	-0.17*

AHI=Apnoea+hypopnoea index; PASAT=Paced auditory serial addition task; SURT=Simple unprepared reaction time; *p<0.05; **p<0.01; ***p<0.001

Breathing pattern

AHI significantly, but weakly, correlated with performance IQ, i.e. higher disease severity was associated with a lower performance IQ (Figure 5.20). No other cognitive function score significantly related to AHI (Table 5.8).

Figure 5.20; Scatterplot of AHI versus performance IQ ($\rho=-0.17$, $p=0.04$)



Oxygenation

Measures of hypoxaemia also significantly correlated with reaction time gaps and performance IQ (Figures 5.21 & 5.22), and also correlated with trail making B, IQ decrement, PASAT (4 secs) and digit symbol scores (Table 5.8). All significant relationships were in the expected direction, i.e. lower oxygen saturation levels were associated with poorer performance scores.

Figure 5.21; Scatterplot of % minimum oxygen saturation versus performance IQ ($\rho=0.19$, $p=0.02$)

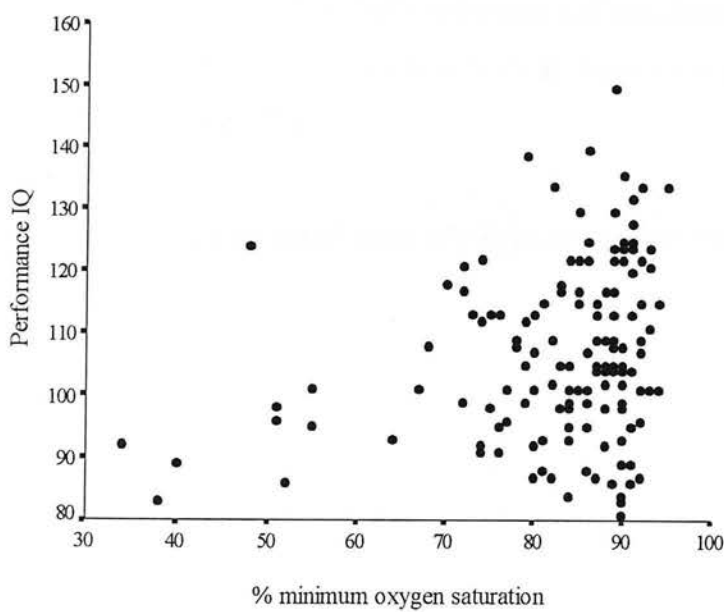
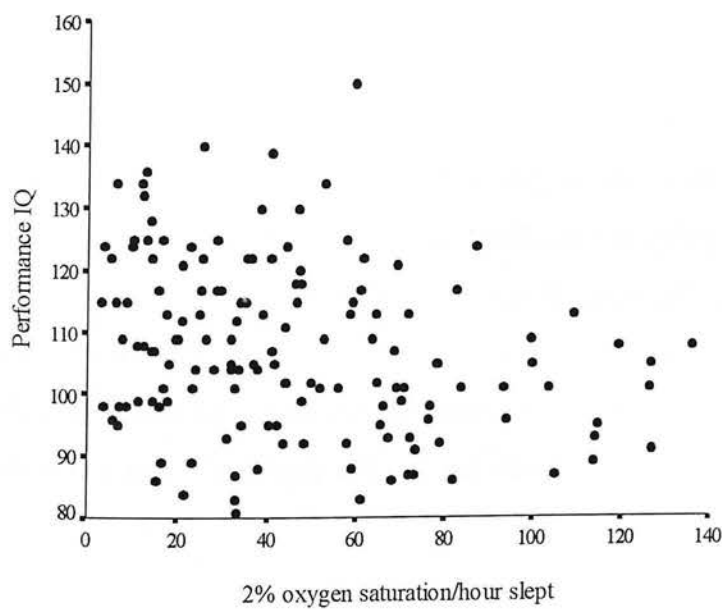


Figure 5.22; Scatterplot of 2% desaturations versus performance IQ ($\rho=-0.23$, $p=0.005$)

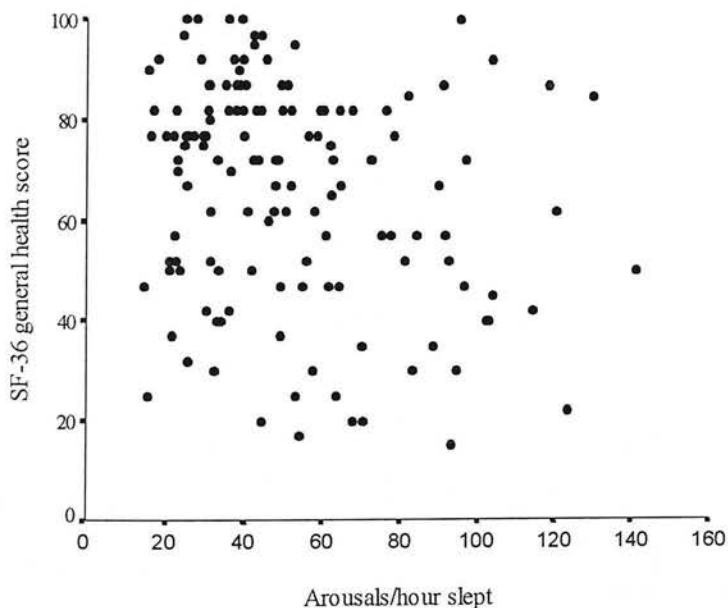


5.3.3 Relationships with self-ratings of daytime function

Sleep quality

Arousal frequency weakly, but significantly, correlated with SF-36 measures of general health (Figure 5.23), health transition and the physical components summary (PCS) scores (Table 5.9), i.e. a higher arousal frequency was associated with a poorer functional status outcome.

Figure 5.23; Scatterplot of arousal frequency versus SF-36 general health score ($\rho=-0.24$, $p=0.005$)



No relationships were found between % sleep stages or sleep continuity and self ratings of daytime function. TST was significantly correlated with SF-36 general health ($r=0.18$, $p<0.05$). SSWI was also significantly correlated with SF-36 physical components summary ($r=-0.20$, $p<0.05$), and SF-36 general health ($r=-0.19$, $p<0.005$). These significant correlations were in the expected direction of better sleep quality associated with higher functional status scores.

Table 5.9; Spearman rank correlation matrix of relationships between nocturnal SAHS arousal, breathing and oxygenation measures and self-ratings of daytime function. All correlations are controlled for age and awake oxygen saturation

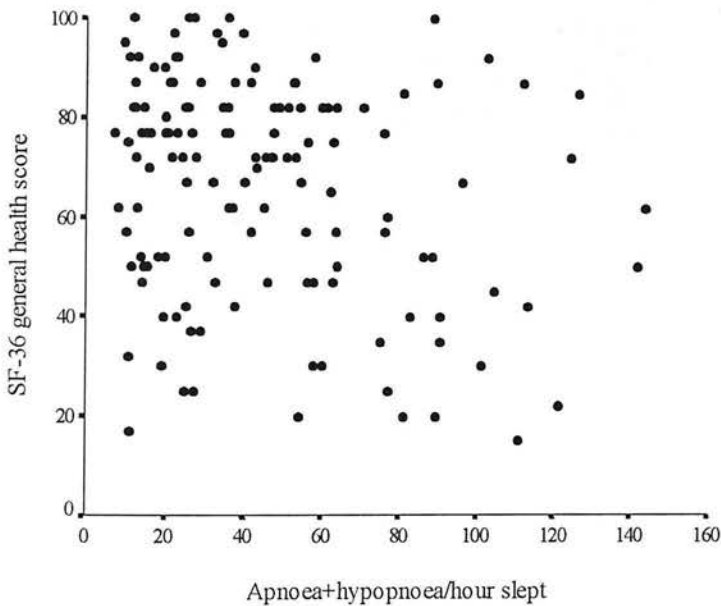
	Arousal	AHI	2% desats	3% desats	4% desats	min sat
ESS	0.03	-0.04	0.06	0.07	0.06	-0.22*
EPQR -Extraversion	0.03	0.06	0.00	-0.02	-0.03	0.04
EPQR -Lie scale	-0.12	-0.10	-0.02	-0.03	-0.05	0.09
EPQR -Neuroticism	-0.12	-0.15	-0.05	-0.06	-0.06	0.00
EPQR -Psychoticism	-0.06	-0.04	0.07	0.03	0.01	-0.01
HAD -Anxiety	-0.02	-0.05	-0.01	0.00	-0.02	0.00
HAD -Depression	-0.05	-0.04	0.08	0.11	0.12	-0.21*
NHP part 2	-0.02	0.05	0.16	0.19*	0.19*	-0.26**
SAHS symptoms	0.10	0.16	0.23**	0.27**	0.27**	-0.33***
SF36 - PCS	-0.22*	-0.20*	-0.20*	-0.23**	-0.23**	0.21*
SF36 - MCS	0.13	0.02	-0.06	-0.02	0.00	0.12
SF36 - general health	-0.24**	-0.22*	-0.29**	-0.28**	-0.27**	0.25**
SF36 - health trans	0.20*	0.24**	0.29**	0.28**	0.28**	-0.25**
SF36 - physical func	-0.09	-0.08	-0.18*	-0.23**	-0.22**	0.22*
SF36 - social func	-0.01	-0.05	-0.09	-0.11	-0.10	0.17*
SF36 - bodily pain	-0.05	-0.07	-0.04	-0.04	-0.05	0.12
SF36 - mental health	0.11	0.05	-0.05	0.00	-0.01	0.08
SF36 - role emotional	0.09	0.00	-0.05	0.00	0.03	0.04
SF36 - role physical	-0.10	-0.14	-0.14	-0.15	-0.15	0.12
SF36 - vitality	-0.05	-0.16	-0.22*	-0.25**	-0.25**	0.32***
SSS	0.03	0.04	0.07	0.10	0.12	-0.13

AHI=Apnoea+hypopnoea index; ESS=Epworth sleepiness scale; EPQR=Eysenck personality questionnaire (revised); HAD=Hospital anxiety and depression (scale); NHP=Nottingham health profile; PCS=Physical components summary; MCS=Mental components summary; SSS=Stanford sleepiness scale; *p<0.05; **p<0.01; ***p<0.001

Breathing pattern

AHI significantly, but weakly, correlated with the same quality of life measures as the arousal frequency (Table 5.9; Figure 5.24), but with no other self reported daytime measures.

Figure 5.24; Scatterplot of AHI versus SF-36 general health score ($\rho=-0.22$; $p=0.01$)



Oxygenation

Measures of hypoxaemia significantly correlated with a range of self ratings of daytime function, although all significant correlations were weak, each explaining less than 8% of the variance (Table 5.9; Figures 5.25 & 5.26).

Figure 5.25; Scatterplot of % minimum oxygen saturation versus SF-36 general health score ($\rho=0.25$, $p=0.003$)

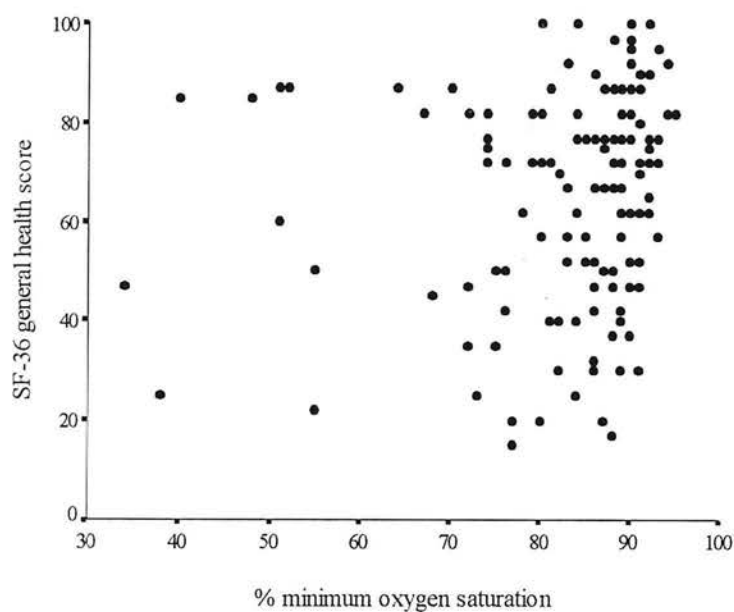
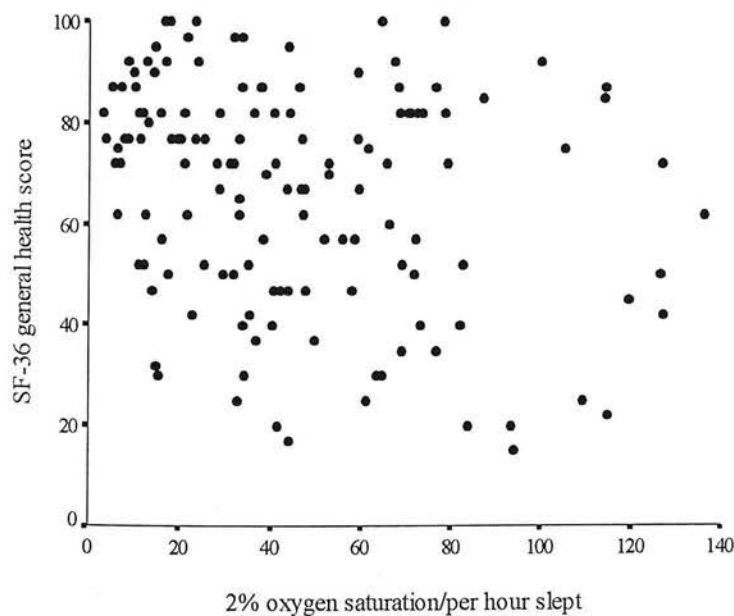


Figure 5.26; Scatterplot of 2% oxygen desaturations versus SF-36 general health score ($\rho=-0.29$, $p=0.001$)



Multiple regression analysis

Seven self rating scales significantly correlated with multiple nocturnal SAHS variables. For these self rating scales, a stepwise multiple regression analysis was performed on ranked data. In each case the variance revealed by the analysis represents the percentage variance after forcing in age and awake oxygen saturation levels (i.e. regardless of the order of entering age and wake oxygen saturation). In the multiple regression of SF-36 physical components summary, with arousals, AHI, 2, 3, 4% desats and the minimum oxygen saturation, the arousal frequency was identified as the single independent predictor of SF-36 PCS. However, the arousal frequency only accounted for 7% of the explained variance. The 2% oxygen desaturation index was the single independent predictor for the SF-36 health transition (10% of variance) and general health (8% of variance) scores. The 3% oxygen desaturation index was identified as the single predictor of SF-36 physical functioning (10% of variance). The minimum oxygen saturation was associated with self rated symptoms (9% of variance), SF-36 vitality (12% of variance) and the NHP score (8% of variance).

5.4 Discussion

This study has demonstrated that conventional variables measured from routine polysomnography do not closely relate to impairments in daytime function in SAHS patients. In previous correlational studies moderate or weak relationships were reported. The current study differs from previous correlational studies in terms of the sample size used, the design and the outcomes assessed. Previous studies can be criticised for recruiting small patient samples (Roth et al 1980, Stepanski et al 1984, Greenberg et al 1987, Bedard et al 1991b, Cheshire et al 1992, Findley et al 1986, Borak et al 1996), and in some cases recruiting only selected severe patients (Roth et al 1980, Bedard et al 1991b). The current study improved on this by recruiting a large, consecutive, unselected patient population with wide ranging disease severity. In addition, this study controlled for age and awake oxygen levels in all correlations. It is well known that age (Lezak 1983) and awake oxygen saturation (Grant et al

1982) affect daytime function. In the current study, age significantly correlated with a range of nocturnal and cognitive function variables, self rating questionnaires and the mean MWT. Awake saturation significantly correlated with cognitive function measures. Of the correlational studies reviewed in Chapter 2, only Cheshire et al (1992), Yesavage et al (1985) and Kim et al (1997) controlled for age in their correlational analysis. Previous studies have also examined only a small number of nocturnal variables and outcome measures in their analysis. This may be to avoid multiple comparisons, and therefore type 1 error, for which the current study could be criticised. However, by limiting the variables measured, the significant relationships reported may be of a lower predictive value than another variable not measured, due to colinearity.

5.4.1 Relationships with measures of daytime sleepiness

Sleep Quality

The major hypothesis, that microarousals from sleep cause daytime sleepiness, was not proven. This result is in keeping with previous small studies (Stepanski et al 1984, Cheshire et al 1992). Stepanski et al (1984) examined correlations between arousal and daytime sleepiness, as measured by the MSLT, in 15 sleep apnoeics. No significant relationship was found. The arousal definition included brief increases in EEG and EMG frequency. Cheshire et al (1992) used the arousal definition defined in Chapter 3, and found no significant relationship with MSLT measured sleepiness in 29 patients. However, the sample sizes in these studies were small. In contrast, studies have also reported significant correlational relationships between arousals and daytime sleepiness (Roehrs et al 1989, Poceta et al 1992). Roehrs et al (1989) examined correlational relationships between nocturnal SAHS measures and daytime sleepiness, as measured by the MSLT, in 466 SAHS patients. Multiple regression analysis found the nocturnal measure of respiratory related arousals (RAR) to be the best single predictor of daytime sleepiness. However, this moderate relationship explained less than 13% of the residual variance, a level at which clinical relevance is questionable. Roehrs et al (1989) defined RAR's as ≥ 3 second increases in EEG frequency or increases in EMG (or both), occurring at the termination of a respiratory event. This

definition of arousal frequency does not require a change in EEG frequency and therefore may be underestimating the degree of sleep fragmentation. Similar findings were presented by Poceta et al (1992) who examined the relationships between nocturnal SAHS measures and MWT measured sleepiness in 322 patients. Again, multiple regression analysis found respiratory related arousals to be the best predictor of daytime sleepiness, although explaining less than 13% of the variance. The criteria for scoring respiratory related arousals in that study (Poceta et al 1992) were not defined, and so is difficult to compare with the current findings. Many other correlational studies did not measure microarousals (Roth et al 1980, Guilleminault et al 1988b, Bedard et al 1991b, Chervin et al 1995). Therefore the contribution of microarousals as predictors of daytime sleepiness is unknown. In terms of study design, the current study was most similar to that of Cheshire et al (1992), with the addition of the MWT. The current study has confirmed those previous findings in a larger sample size.

In the current study, paradoxical relationships were found between nocturnal sleep quality and continuity measures and objective daytime sleepiness. Previous studies have found mixed results with measures of sleep quality. Guilleminault et al (1988b) found significant relationships with SWS and % stage 1 and MSLT latencies in the expected direction. Roehrs et al (1989) measured a sleep parameter, only identified as 'PSG1' (possibly stage 1 sleep) which correlated significantly with MSLT. Roehrs et al (1989) and Poceta et al (1992) also measured TST, which did not significantly relate to daytime sleepiness, although both of the r values were paradoxically negative, as in the current study. In large number studies, little predictive information is derived from sleep stage data.

The smaller number studies (Roth et al 1980, Bedard et al 1991b, Cheshire et al 1992, Chervin et al 1995) found no significant relationships with sleep stage variables and nap latency. A significant paradoxical relationship was reported in Roth et al's (1980) 10 normal subjects. Percentage wake positively correlated with latency to stage 1 on the daytime naps. This paradoxical result from Roth et al's small study is supported by

recent data on the MWT in 64 normal subjects (Doghramji et al 1997). In a normative study, Doghramji et al (1997) observed no relationship between TST and MWT, but a paradoxical relationship was found between sleep efficiency and MWT ($r = -0.31$, $p < 0.05$). Roth et al (1980) explained their paradoxical findings by suggesting that, at least in normal subjects, sleep onset is 'set' to some degree, regardless of nocturnal sleep patterns. Harrison & Horne (1996b) have since termed this phenomenon 'sleepability', suggesting that some individuals have the ability to 'switch off' and sleep in a strange place on demand, despite having no daytime sleepiness or sleep debt. Does the same hold true for sleep apnoeics, where some individuals slept well at night and in the daytime under lab conditions, regardless of disease severity? There is no explanation for these paradoxical findings, except to speculate that the current study population may also contain individuals with different sleepiness thresholds.

Breathing Pattern

AHI did not significantly relate to objective daytime sleepiness. This is in agreement with the small correlational studies performed by Cheshire et al (1992) in 29 patients, and Chervin et al (1995) in 28 SAHS patients. The larger sample study of Guilleminault et al (1988b) in 100 SAHS patients found no significant relationships between AHI and the MSLT. The small sample studies by Roth et al (1980) and Bedard et al (1991b) also found no association, but only measured apnoeas, not hypopnoeas, so cannot be directly compared. Conversely, Poceta et al (1992) found the RDI to significantly correlate with MWT, although the authors suggest that this relationship may be due to the intercorrelation with measures of hypoxaemia. In addition, the RDI is not defined in their paper, so whether a coexisting desaturation is required, is not known. Roehrs et al (1989) also found the breathing pattern (AI) to significantly correlate with the MSLT. Both apnoeas and hypopnoeas were quantified by airflow reduction criteria rather than inductance plethysmography and therefore may be underestimated.

Oxygenation

The minimum oxygen saturation significantly correlated with MWT. The relationship was weak and could be a type 1 statistical error due to the multiple comparisons made between PSG measures and objective daytime sleepiness. However, Bedard et al (1991b) also found a significant relationship between the MSLT and minimum oxygen saturation. As with AHI, the large number studies of Roehrs et al (1989) and Poceta et al (1992) also found significant relationships between measures of hypoxaemia and objective sleepiness. In their multiple regression analysis, Poceta et al (1992) found the mean oxygen saturation level to contribute to objective sleepiness, whereas Roehrs et al (1989) reported that hypoxaemia did not add important information to the existing relationships with arousal and AHI and daytime sleepiness.

The lack of significant relationships between the ESS and AHI and arousal measures are in keeping with the findings of Chapter 4, and again contrasts with the work by Johns (1993), where significant relationships were found between the ESS and AHI ($r=0.4$, $p<0.001$) in 165 SAHS patients. However, in agreement with the current study, Johns (1993) also found a significant relationship between minimum oxygen saturation and ESS. In John's study (1993), the AHI scoring criteria included an associated criteria of at least a 3% oxygen desaturation, thus Johns' patient sample may represent a more severe group than the current study. This may explain the differing results.

5.4.2 Relationships with cognitive function measures

In agreement with earlier studies, arousal frequency, sleep stage variables, AHI and especially measures of hypoxaemia weakly predict decrements in cognitive performance (Greenberg et al 1987, Bedard et al 1991b, Cheshire et al 1992).

The arousal frequency was only associated with one cognitive function measure of information processing time. Cheshire et al's (1992) small number study found the arousal frequency to relate to a measure of visuospatial organisation. Other studies on

SAHS clinic patients (Yesavage et al 1985, Greenberg et al 1987, Bedard et al 1991b) and in the community (Kim et al 1997) did not measure microarousal frequency and so comparisons cannot be made.

The current study also reported 6 significant relationships between measures of sleep quality and cognitive performance. Although significant, these relationships were weak, each explaining less than 6 % of the variance. There were 108 possible relationships sought between sleep quality and cognitive function, therefore 5 significant associations would be expected by chance alone. Cheshire et al (1992) found % REM sleep to relate to simple reaction time and Bedard et al (1991b) found awakenings and stage shifts to wake to significantly correlate with choice reaction time, however, Bedard et al (1991b) did not control for age in their correlations.

AHI was associated with one measure of performance IQ. In agreement, Cheshire et al (1992) found AHI to relate to measures of IQ, and Yesavage et al (1985) found AHI to relate to tests measuring visuospatial reasoning, memory and psychomotor speed. As in the current study, both Cheshire et al (1992) and Yesavage et al (1985) controlled for age in their correlations. This result is compatible with a recent large scale population study of 841 individuals, reporting significant, but weak, age-controlled relationships between AHI and psychomotor efficiency (Kim et al 1997). These authors did not present results for arousals and measures of hypoxaemia, so no comparisons with these measures can be made.

In this study, measures of hypoxaemia weakly predicted decrements in mental flexibility, performance IQ, attention and response speed. Bedard et al (1991b) found a strong relationship between hypoxaemia and attention, explaining 58% of the variance. However, Bedard et al (1991b) used a selected sample of moderately severe patients with an inclusion criteria of a minimum oxygen saturation ≥ 80 % and did not control for age or awake saturation levels in the correlations. Cheshire et al (1992) found hypoxaemia to be associated with reaction time, coding speed and IQ, which are functional areas similar to those reported in the current study. Greenberg et al

(1987) only reported 4/72 significant relationships between hypoxaemia and cognitive function tests, and these relationships could be due to chance alone.

The current study is the largest correlational study to measure a wide range of nocturnal SAHS measures and cognitive function tests in SAHS patients, and in agreement with the recent large scale population study by Kim et al (1997), weak relationships between nocturnal measures and cognitive function were identified.

5.4.3 Relationships with self ratings of daytime function

Nocturnal SAHS measures significantly related to a whole range of self ratings of daytime function, although the correlations identified were weak, in no case explaining more than 12 % of the observed variance. The stronger correlations were associated with oxygen saturation measures rather than measures of arousal, AHI, TST or SSWI. A similar pattern was also seen in the multiple regression analysis. Significant relationships with hypoxaemia were most frequently found with the questionnaire self reports of vitality, symptoms, general health and physical well-being. These somatic items may be the area in which the patient is most aware of noticing a decrement. In agreement with the current study, Smith & Shneerson (1995) also examined ratings on the SF-36 questionnaire in snorers and SAHS patients and found 4% desaturations weakly correlated with physical function, general health and vitality. The authors speculated that if measures of sleep fragmentation had been made in their study, stronger relationships with quality of life may have been observed, but this was not found in the current study.

Relationships were not found between nocturnal SAHS measures and the EPQR personality measures, HAD anxiety or the SF-36 mental health and emotional role dimensions. As mentioned above, the measures of physical functioning may be most prevalent in the eyes of the patient, who notices when he can't walk over a mile, while changes in personality and mood may be less noticeable. A significant relationship was found between minimum oxygen saturation and the HAD depression rating. This is in

contrast to the studies by Millman et al (1989) and Borak et al (1996) who found no significant relationships between hypoxaemia and depression using the Zung self rating depression score and Beck's depression rating, respectively. The HAD contains one depression statement which could be interpreted as being sleepy i.e. 'I feel as if I am slowed down', and this may explain the relationship with the HAD scale. However, the Zung self rating depression scale also contains questions about fatigue, task performance and sleep disruption and demonstrated no relationship with nocturnal SAHS measures.

This study found no relationships between nocturnal SAHS variables and the Stanford sleepiness scale (SSS). This is in accord with previous reports on the poor nocturnal relationships with the SSS (Dement et al 1978, Roth et al 1980) in SAHS patients.

In summary, the current findings are difficult to compare with previous studies due to differences in methodology. Where comparisons can be made, there is both agreement and disagreement with previous findings. The main message from the current study is the lack of clinical PSG predictors of daytime dysfunction in SAHS patients. The following section goes on to further discuss the pros and cons of the current study design and to provide further evidence in support of the lack of significant relationships found.

5.4.4 General discussion

Multiple comparisons

One potential criticism of this study is the large number of correlations performed. A total of 525 correlations were sought. Given this, it is inevitable that some of the 72 significant correlations observed are due to chance alone, but only 26 such chance observations would be expected ($525/20$) given the significance value set at 0.05 in the current study. However, the main message of this study is not the number of significant correlations, but the weakness of the correlations observed. In fact significant relationships between nocturnal SAHS measures and daytime function all

explained less than 12% of the observed variance. There are a number of possible reasons for the lack of strong correlational relationships in the current study.

Signal and scoring reliability

The significant relationships between hypoxaemia and daytime function were stronger and more frequent than with other nocturnal measures in both correlational and multiple regression analyses. It is possible that hypoxaemic variables are the true causative factors of daytime function. Alternatively, this could be due to methodological factors. Oximetry is a reliable measure. It requires one channel of signal recording with good feedback if the signal is poor or the probe has fallen off. The scoring of oximetry is computer derived and so is highly reproducible. Conversely, the microarousal requires channels of EEG and EMG and is more susceptible to poor quality signal, as are the respiratory channels, with position influencing the quality of plethysmography traces, particularly in the obese patient. Scoring of both the AHI and microarousal frequency requires the following of strict criteria, which are always going to have a subjective element (Section 3.3 on reproducibility scoring). However, evidence suggests that reproducibility is good, at least for the definitions of arousal (Martin et al 1997c) and AHI (Whyte et al 1992) used in this thesis. Variation in signal reliability may also be the reason for Bedard et al (1991b) finding relationships with hypoxaemia and MSLT, and not with sleep stage variables or apnoea frequency.

Arousal definition

As mentioned previously, this thesis used the Cheshire arousal definition (Cheshire et al 1992). Using an in-house measure of sleep fragmentation may explain the weakness of the relationships in the current study. This is not likely to be the case, as the Cheshire definition has been well-validated against itself and other arousal measures, including the standard ASDA definition (Martin et al 1997c).

The two large scale correlational studies (Roehrs et al 1989, Poceta et al 1992) which found significant relationships between arousals and objective sleepiness in SAHS

patients, both used definitions of respiratory related arousals. In the current study, all arousals were scored and used in the subsequent analysis, regardless of whether or not they were associated with an apnoea or hypopnoea. All arousals have the ability to cause daytime dysfunction, and it was the effect of sleep fragmentation on daytime function, that was the main hypothesis of the study. In addition, so called 'spontaneous' arousals may in fact be associated with a snore crescendo or a period of increased respiratory effort which are not scored routinely, yet have been reported to affect daytime function (Guilleminault et al 1991, 1993).

MSLT and MWT

The MSLT and MWT are considered as 'gold standards' for measuring daytime sleepiness. However both the MSLT and MWT are susceptible to influences other than physiological sleepiness levels. The MWT is highly susceptible to motivational factors, and instructing an individual to 'try and stay awake' may activate a whole range of physiological processes such as motivation (Poceta et al 1992) competitiveness (Roehrs & Roth 1992) and attention ability (Poceta et al 1992). Interestingly, motivational factors have also been reported to effect the MSLT. Harrison et al (1996c) compared MSLT latency in two groups of normal subjects, both of whom completed baseline MSLTs under standard instructions. Then on a second occasion, one group was given financial incentives to 'fall asleep quicker than the last time', and the other group normal instructions. The incentive group fell asleep significantly faster than the non-incentive group. Such psychological influences as these are likely to vary between individuals, regardless of disease severity. Other measures of daytime sleepiness and alertness, such as behavioural tasks (Bennett et al 1997), or monitoring for EEG microsleeps during an individuals daily routine may prove more useful in the future (see Chapter 9).

Study population

The population studied represent a heterogeneous, unselected, consecutive sample, both in terms of SAHS severity and age. This was done deliberately in order to provide the wide variance required to investigate potential correlations. The current sample included 23 individuals with AHI's in the 5-15 range. This was due to previous work identifying that mild patients demonstrate daytime dysfunction (Young et al 1993 & 1997, Kim et al 1997), which can be improved with CPAP therapy (Engleman et al 1997a).

To be included in the study, patients had to have an ESS \geq 8 and/or at least 2 other features of SAHS. Patients therefore did not have to be excessively sleepy, in terms of their ESS, to participate in the study. This was to avoid excluding sleepy patients, who have lost their frame of reference, and underestimate their score on the ESS (Chapter 4; Engleman et al 1997b). The fact that not all patients had an ESS \geq 8 may have contributed to the mean MSLT SOL of 9.7 minutes, compared to a mean value of 6 minutes in Roehrs et al's (1989) SAHS sample. However, both of these mean MSLT values, and those in other studies (Guilleminault et al 1988b, Bedard et al 1991b, Sangal et al 1992a, Cheshire et al 1992) lie within the 'grey zone' of latencies between 5-10 minutes. The studies that did find relationships between arousals and MSLT (Roehrs et al 1989, Poceta et al 1992) do not define any prior sleepiness criteria for inclusion in their studies, making comparisons difficult. However, sleepiness is more likely to have been a dominant clinical feature in these earlier studies. In all other aspects the patients in the current study were typical of an unselected SAHS population. Patients had a mean AHI of 45, mean BMI of 32 and an MWT latency of 27 minutes, which was very similar to Poceta et al's (1992) value of 26 minutes.

To identify if relationships were not found in the current study due to the inclusion of patients with an AHI in the 5-15 range, and an ESS $<$ 8, a post-hoc analysis was undertaken. A subgroup of patients (n=75) with both an AHI \geq 15 and ESS \geq 11(2SD above the normal mean level; Johns & Hocking 1997) were examined. The results

demonstrated that even in this subgroup, MSLT and MWT mean SOLs and ESS did not significantly correlate with measures of AHI, arousals and hypoxaemia (all $p < 0.2$, $p > 0.12$).

Study Protocol

The patients performed their daytime tests after a normal night's sleep at home and not on the day following overnight polysomnography. This is a potential criticism of the study, as this is not standard (Carskadon et al 1986). There were several reasons for this. Most importantly, this study wanted to examine how the sleep study results related to daytime function decrements in patients during a normal day, and not after a polysomnography (PSG) disrupted night. It is the level of daytime decrements experienced every day that need to be abolished with CPAP therapy, not PSG induced ones, thus these are the values which need measuring. Secondly, this study was designed to follow the same protocol as the previous correlational study by Cheshire et al (1992), who also performed the MSLT after a normal night's sleep at home. Thirdly, due to the design of the protocol, an elapse of time was needed to allow for the scoring of the PSG records to confirm that patients had an $AHI \geq 5$ and no coexisting sleep disorders (e.g. PLMS). As Cheshire et al (1992) also found no significant relationships with PSG variables and MSLT, it is possible that performing the daytime tests after a night's sleep at home could explain the current findings. It would have been useful to measure actimetry on patients on the night prior to their daytime tests to achieve an estimate of sleep quality and quantity with minimal interference. This question of performing tests after a night at home is the theme of Chapter 8 of this thesis, where an experiment compared objective sleepiness after a night at home and a night in the sleep centre.

Another possible reason for the patients not being particularly sleepy in terms of their MSLT, is that the test day involved a busy schedule, and therefore may have increased alertness levels. When only an MSLT is performed on a day, it is a very long, monotonous and sedentary day, and it might be suggested that this could increase sleepiness levels compared to a normal working day. However, evidence suggests that

a behavioural activity will increase, rather than decrease sleepiness (Horne & Minard 1985b, Kribbs et al 1994). For example, Horne & Minard (1985b) demonstrated in normal subjects that an active day caused an increase in subjective sleepiness compared to a monotonous lab based day. In agreement, Kribbs et al (1994) compared 10 minute nap opportunities before and after normals performed a vigilance task. Nap latency was found to decrease after the brief performance task. This evidence does not explain the MSLT of 9.7 minutes. Furthermore, the current daytime testing schedule more closely resembled a normal day, with both active and sedentary tasks. Previous studies have successfully performed the MSLT and MWT on the same day (Sangal et al 1992a & 1992b, Martin et al 1996, 1997b), with Martin et al (1996) finding significant changes in both the MSLT and MWT with experimental sleep fragmentation.

Conclusion

A correlational study involves analysis across patients and this is likely to maximise sample variance. It is probable that there are many unknown factors affecting daytime function in addition to the hypothesised sleep fragmentation. For example, it is possible that patients have differing thresholds for their level of inherent sleepiness, that is, their level of sleep need regardless of disease severity. In addition, sleepiness is context dependent and although patients perform the MSLT/MWT under identical conditions, they may differ in terms of their 'sleepability' (Harrison & Horne 1996b) and their normal daily routines. For example, some individuals find napping in the daytime unusual due to work and personal commitments, whereas others nap on a daily basis. Some patients may find alertness is increased due to the anxiety associated with undergoing these tests. Adaptation to SAHS is another factor. Some patients may adapt to their disease using behavioural means, by learning coping strategies to stay awake during monotonous tasks, or have the ability to upgrade performance and attention when necessary. Others may be physiologically adapted to their disease. For example, patients may have higher arousal thresholds. These could be patients who have had their condition for a long time, or have very severe disease, or who are pathologically sleepy in the daytime and therefore cannot afford to further disrupt

sleep. Experimental modelling studies (Colt et al 1991, Martin et al 1996, Brooks et al 1997) may overcome some of the methodological problems of correlational type studies. Modelling studies have the advantage of allowing the nocturnal variables to be studied in isolation. For example, using the randomised crossover protocol described by Colt et al (1991), the current study could be repeated with patients administered CPAP to abolish all events on one limb, and on the other limb, patients could be administered CPAP plus 100% nitrogen to induce hypoxaemia in isolation, followed by daytime testing, to examine the effects of hypoxaemia alone on daytime function. In addition, modelling studies can often be performed on normal subjects (Martin et al 1996) or animals (Brooks et al 1997) and therefore reduce some of the interindividual variability specific to the SAHS patient group, such as the duration of their disease and the varying adaptation to it. Also using a crossover study design (Colt et al 1991, Martin et al 1996) allows each subject to be their own control, again reducing interindividual variability. Further modelling studies on larger sample sizes are required to determine the factors affecting daytime function in SAHS.

Chapter 6

Interrelationships Between Measures of Daytime Function in SAHS

6.1 Introduction

This chapter focuses on the interrelationships between measures of daytime function in the sample of 150 SAHS patients previously described (Section 5.2). In particular, the relationships between the two measures of objective sleepiness, the MSLT and MWT, and their relationship with measures of cognitive performance and psychopathology are investigated.

The first aim of this chapter was to repeat the comparison between the MSLT and MWT performed by Sangal et al (1992a), however, this time in a population solely comprised of SAHS patients. The second aim of this study was to compare both the MSLT and MWT to a diverse battery of psychometric measures with the hypothesis that the MWT demonstrates stronger relationships with other measures of daytime function and is therefore the more appropriate test to reflect baseline daytime function in SAHS patients.

Previously, Sangal et al (1992a) closely examined the relationship between the MSLT and MWT, when performed on the same day. This was in a sample of 258 patients with disorders of excessive somnolence, of which 170 were sleep apnoeics. The study demonstrated a moderately strong correlation between the MSLT and MWT ($r=0.41$, $p<0.001$). However, when considering that these tests both measure EEG sleep onset, this moderate correlation suggests that the two tests may be measuring different physiological abilities of sleepiness and alertness, respectively.

Previous studies have also compared the MSLT to self reports of daytime function. As part of the validation work on the ESS, two studies by Johns (1991, 1994) examined relationships between the ESS and the MSLT. In the first study (Johns 1991), using 27 patients with disorders of excessive somnolence, a significant

relationship was found between the ESS and MSLT ($r = -0.5$, $p < 0.01$). However, only two of the 27 patients were diagnosed with SAHS. In the second correlational study by Johns (1994), 44 patients with excessive daytime sleepiness were studied, this time using a Spearman rank correlation. In agreement, a significant relationship was found between the ESS and MSLT ($\rho = -0.42$, $p < 0.01$). Again only a small proportion of the patients were diagnosed with SAHS ($n = 8$). Chervin et al (1997) performed a similar study in a group of 60 patients with disorders of excessive sleepiness, of which 23 were sleep apnoeics. There was a significant Spearman correlation of $\rho = -0.37$, $p = 0.004$ between the ESS and MSLT. The above studies demonstrate moderately strong relationships between the ESS and the MSLT in a population of patients with a range of sleep disorders.

In a community based study, Briones et al (1996) examined daytime relationships in 129 individuals, using the general health measures of the SF-36, ESS and MSLT. The subjects consisted of normal controls, snorers and patients with sleep disordered breathing (total population mean \pm SD RDI of 8 ± 7 /hour slept). Results demonstrated that the ESS significantly correlated with SF-36 scores for general health, vitality and emotional role, whereas the MSLT only significantly related to SF-36 vitality ($r = -0.19$, $p = 0.02$). The ESS and MSLT were also significantly, but weakly, related to one another ($r = -0.27$, $p < 0.05$).

The current study further examines interrelationships between daytime function measures, by examining a wide range of daytime tests in a large, consecutive SAHS sample.

6.2 Methods

6.2.1 Patients and protocol

The 150 patients involved in the study and the methods used have been described earlier (Sections 3.4, 3.5, 5.2). The daytime interrelationships examined are shown in Table 6.1.

Table 6.1; Table of the daytime interrelationships examined

1. MSLT versus MWT

2. MSLT and MWT versus self reports of daytime function:-

Epworth sleepiness scale
Stanford sleepiness scale
Nottingham health profile (part 2)
Hospital anxiety & depression scale
SAHS symptom ratings
SF-36 - physical components summary
SF-36 - mental components summary
SF-36 - vitality
SF-36 - general health
SF-36 - social function
SF-36 - physical function
SF-36 - role emotional
SF-36 - role physical
SF-36 - bodily pain
SF-36 - mental health
SF-36 - health transition
Eysenck personality scale - neuroticism
Eysenck personality scale - psychoticism
Eysenck personality scale - lie scale
Eysenck personality scale - extraversion

3. MSLT and MWT versus cognitive function tests:-

Block design
Digit symbol
Performance IQ
IQ decrement
Paced auditory serial addition task (PASAT) 2 sec
Paced auditory serial addition task (PASAT) 4 sec
Trail making A
Trail making B
% Steer Clear cow hits
Simple unprepared reaction time - mean
Simple unprepared reaction time - false response
Simple unprepared reaction time - no. of gaps

6.2.2 Statistics

Many of the daytime variables were non-normally distributed, therefore non-parametric correlational statistics were used throughout for consistency. Relationships between daytime function measures were evaluated by Spearman rank correlation coefficients. Age significantly correlated with the MWT ($\rho=0.27$, $p=0.001$), and eleven self reports of daytime function (all $\rho>0.15$, $p<0.05$). In addition, age and awake oxygen saturation significantly correlated with nine cognitive function measures (all $\rho>0.15$, $p<0.05$). Therefore all correlations performed were partial, controlling for age and awake oxygen saturation. Multiple regression analysis on ranked variables was used to identify independent predictors when an outcome measure significantly correlated with more than one putative determinant variable. As previously described (Section 5.2.4), age and awake oxygen saturation were forced into the multiple regression analysis prior to stepwise regression of the significant correlates. All tests were 2-tailed and a probability value of less than 0.05 was accepted as statistically significant. All data were analysed using SPSS for Windows 6.1. The statistically significant results in this chapter are represented in the tables in bold type for clarity.

6.3 Results

6.3.1 MSLT versus MWT

There was a statistically significant relationship between the MSLT and the MWT ($\rho=0.43$, $p<0.0001$) (Figure 6.1). Using the method described by Sangal et al (1992a), the group median of the mean MSLT and MWT values are shown on the scatterplot of Figure 6.1. The graph is divided into four quadrants with areas of concordance and discordance between the two tests. Patients who were concordant for MSLT and MWT scores are represented in the lower left square (sleepy on both the MSLT and MWT), and the upper right square (not sleepy on either the MSLT and MWT). Discordance between the MSLT and MWT is demonstrated by points in the upper left

portion of the graph (sleepy on MWT, but not on MSLT), and by points in the lower right portion of the graph (sleepy on the MSLT, but not on the MWT).

Figure 6.1; A scatterplot of the mean sleep latencies of the MWT versus the MSLT in 150 SAHS patients. The vertical line represents the group median MWT mean sleep latency (30.9 mins), and the horizontal line represents the group median MSLT mean sleep latency (9.2 mins)

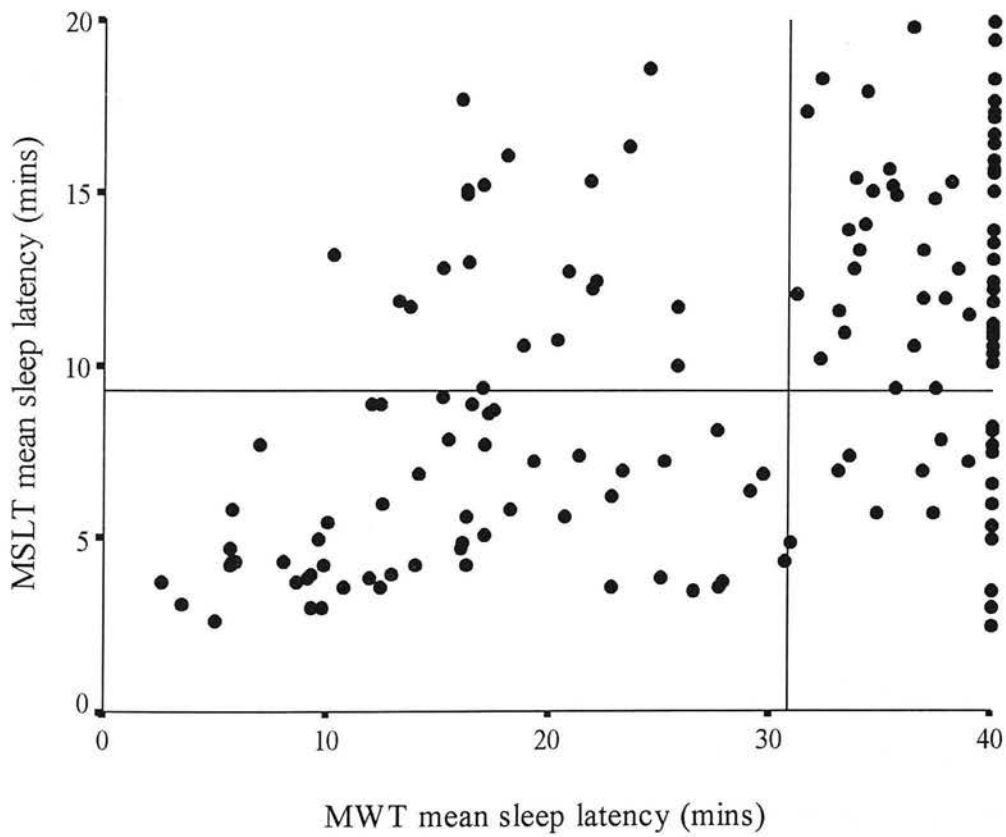


Figure 6.1 shows that a large number of patients had ceiling effects on the MWT. 40 patients did not sleep on all four daytime naps (27%) and on a total of 267/600 MWT naps (45%), no R & K sleep was seen. This contrasts with results from the MSLT, on

which only 1 patient did not sleep on all four naps, and no R & K sleep was seen on a total of 69/600 MSLT naps (12%).

If the correlation between the MSLT and MWT was recalculated without the 40 patients who demonstrated ceiling effects on the MWT, the strength of the correlation increased to $p=0.54$, $p<0.0001$. Therefore to some extent, the ceiling effect on the MWT may be depressing the 'true' correlation coefficient.

The mean (\pm SD) sleep onset latency on the MSLT was 9.7(5) mins, with a range of 2.5 minutes to the maximum of 20 minutes. The mean sleep onset latency on the MWT was 27(12) minutes, with a range of 2.6 to the maximum of 40 minutes.

6.3.2 Objective sleepiness versus self reports of daytime function

The MWT significantly correlated with a range of self reporting questionnaires (Table 6.2). The MWT significantly correlated with ESS measured sleepiness in the expected direction (Figure 6.2). The MWT was also significantly associated with measures of quality of life and well-being, with the sleepier the MWT score, the poorer the level of functional status. However, the MSLT, only correlated significantly, but weakly, with the ESS (Figure 6.3, Table 6.2).

Eight self rating scores significantly correlated with the MWT. For these self rating scores, a stepwise multiple regression analysis was performed on ranked data. The explained variance revealed by the analysis represents that after forcing in age and awake oxygen saturation levels (i.e. regardless of the order of entering age and wake oxygen saturation). In the multiple regression analysis of MWT, the best predictors of the MWT mean latency were the ESS and the SF-36 health transition dimension (together explaining 29% of the variance in MWT).

Table 6.2; Spearman rank correlation matrix of relationships between objective sleepiness and self ratings of daytime function. All correlations are controlled for age and awake oxygen saturation.

	MSLT	MWT
Epworth sleepiness scale	-0.23**	-0.48***
Stanford sleepiness scale	0.11	-0.01
Nottingham health profile (2)	-0.10	-0.31***
HAD - anxiety	0.09	-0.07
HAD - depression	-0.03	-0.22*
SAHS symptom ratings	-0.04	-0.22*
SF-36 - physical components summary	0.02	0.23**
SF-36 - mental components summary	0.06	0.16
SF-36 - vitality	0.07	0.14
SF-36 - general health	0.02	0.12
SF-36 - social function	0.07	0.28**
SF-36 - physical function	-0.01	0.20*
SF-36 - role emotional	0.09	0.12
SF-36 - role physical	0.01	0.13
SF-36 - bodily pain	-0.03	0.14
SF-36 - mental health	-0.05	0.11
SF-36 - health transition	-0.08	-0.28**
Eysenck personality scale - neuroticism	0.10	-0.11
Eysenck personality scale - psychoticism	-0.01	-0.04
Eysenck personality scale - lie factor	-0.05	-0.12
Eysenck personality scale - extraversion	0.02	0.05

MSLT=multiple sleep latency test; MWT=maintenance of wakefulness test; HAD=hospital anxiety and depression scale; *p<0.05; **p<0.01; ***p<0.001

Figure 6.2; Scatterplot of the MSLT versus the Epworth score ($\rho=-0.23$, $p=0.009$)

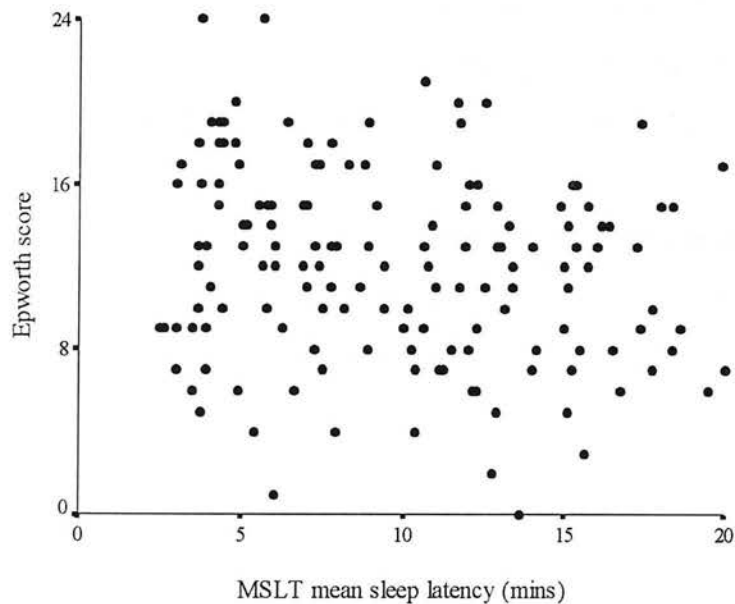
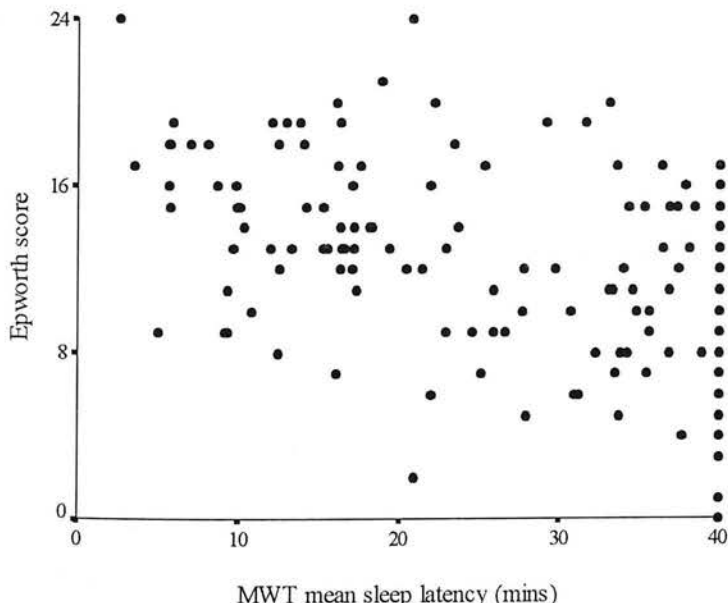


Figure 6.3; Scatterplot of the MWT versus the Epworth score ($\rho=-0.48$, $p<0.0001$)



6.3.3 Objective sleepiness versus cognitive function measures

The MWT significantly correlated with block design, IQ measures, PASAT (4 secs), reaction time (Figure 6.4) and Steer Clear cow hits (Table 6.3). All significant relationships were in the expected direction, i.e. the sleepier the MWT score, the greater the performance impairment. No such significant relationships were found between the MSLT and measures of cognitive function (Table 6.3; Figure 6.5).

Table 6.3; Spearman rank correlation matrix of relationships between objective sleepiness and measures of cognitive function. All correlations are controlled for age and awake oxygen saturation.

	MSLT	MWT
Block design	-0.01	0.20*
Digit symbol	-0.13	0.12
Performance IQ	-0.10	0.22**
IQ decrement	0.02	-0.22**
PASAT (2 seconds presentation)	-0.10	0.06
PASAT (4 seconds presentation)	-0.003	0.17*
Trail making A	0.02	-0.01
Trail making B	0.14	-0.16
% Steer Clear cow hits	-0.13	-0.30***
SURT - mean reaction time	-0.15	-0.32***
SURT - false responses	0.04	-0.05
SURT - frequency of gaps>1 sec	0.03	-0.15

MSLT=multiple sleep latency test; MWT=maintenance of wakefulness test; PASAT=paced auditory serial addition task; SURT=simple unprepared reaction time;

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Six cognitive function tests significantly correlated with MWT. For these cognitive function tests, a stepwise multiple regression analysis was performed on ranked data. The variance explained by the analysis represents the percentage variance after forcing

in age and awake oxygen saturation levels. In the multiple regression analysis of MWT, the best predictors of the MWT mean latency were mean reaction time and the performance IQ (together explaining 17% of variance in MWT).

Figure 6.4; Scatterplot of the MSLT versus mean reaction time
($\rho=-0.15$, $p=0.08$)

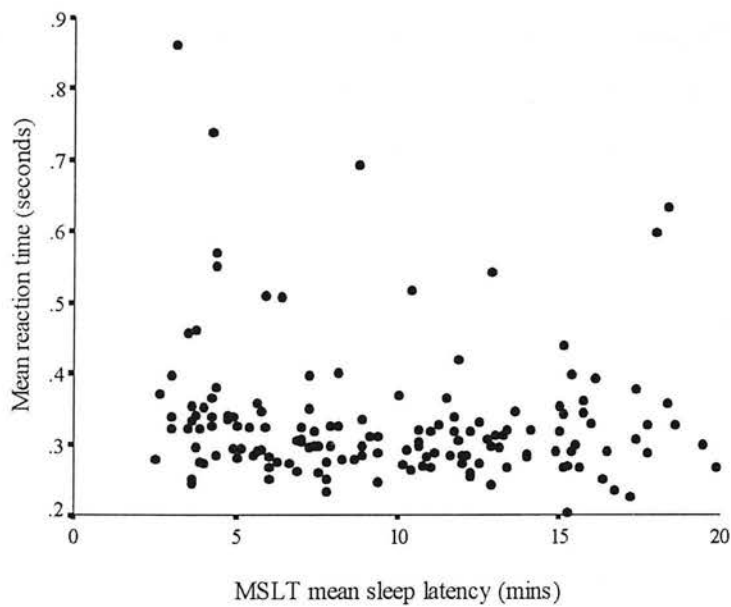
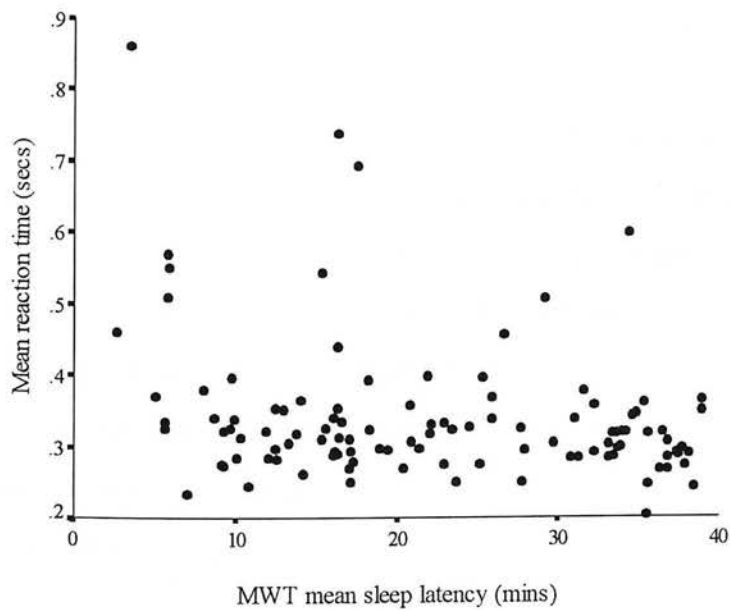


Figure 6.5; Scatterplot of the MWT versus mean reaction time ($\rho=-0.32$, $p<0.0001$)



6.4 Discussion

6.4.1 Relationships between the MSLT and MWT

A significant relationship was found between the MSLT and the MWT, with similar values to those reported by Sangal et al (1992a) in their population of 258 patients with excessive daytime sleepiness. Also in agreement with Sangal et al (1992a), discordance was found between the MSLT and MWT (Figure 6.1). The current study confirms that the MSLT and MWT are likely to be measuring different physiological abilities, otherwise two tests measuring the same outcome variable of EEG defined sleep onset, would be expected to have a higher rho value.

The MSLT and MWT differ in their test instructions of 'to try and sleep' and 'try and stay awake', respectively. This change in instruction lengthened the latency on the MWT, again supporting the idea that the tests measure different abilities. This study population reported a large ceiling effect with the MWT (27%) which was in close agreement with that of Sangal et al (1992a) (29%). This ceiling effect suggests that the MWT is susceptible to high levels of motivation. A post-hoc correlation between MSLT and MWT scores in the 110 patients who did not demonstrate ceiling effects on the MWT resulted in a stronger MSLT/MWT interrelationship. This leads on to the question of whether lengthening of the MWT would have improved the relationship. However, running an MWT for longer than 40 minutes would be too labour intensive and monotonous for patients to undertake.

There are a number of speculative reasons for the discordance found between the MSLT and MWT. Patients that fell asleep quickly on both the MSLT and MWT may either represent individuals who are pathologically sleepy, or individuals with a low motivation level on the MWT. Patients that fell asleep on the MSLT and stayed awake on the MWT may represent patients who are not pathologically sleepy, but have high sleepability when instructed to fall asleep (Harrison & Horne 1996b). Equally, these patients may be pathologically sleepy, but have high motivation to follow instructions, by staying awake on the MWT as instructed. There are many

explanations as to why some patients are sleepy and others not as measured by these objective tests. One further comment is that patients were asked if they felt they had slept at all after the termination of each MSLT/MWT (without feedback). Frequently patients would deny sleeping, when EEG evidence opposed this. It is possible that some patients think they are successfully staying awake on the MWT, when in fact they have fallen asleep, long enough to score sleep onset.

The current study demonstrates in a population of 150 sleep apnoeics, that the MSLT and the MWT do not correlate highly with one another when considering they are both measuring sleep onset latency.

6.4.2 Relationships between objective sleepiness and self reports of daytime function

The MSLT significantly related to the Epworth sleepiness scale. This confirms previous study findings (Johns 1991 & 1994, Briones et al 1996, Chervin et al 1997) in a larger number of sleep apnoeics. In addition, the current sample does not include patients with other disorders of excessive sleepiness (Johns 1991 & 1993, Chervin et al 1997), or normal subjects (Briones et al 1996), thus the relationship presented reflects sleepiness in SAHS patients alone. The current rho value was smaller than those from the previous studies (Johns 1991 & 1994, Briones et al 1996, Chervin et al 1997). This was the only significant relationship found between the MSLT and the 21 self reports of daytime function.

The weak relationships between these two measures of sleepiness may exist because the MSLT and ESS measure different aspects of daytime sleepiness (Briones et al 1996, Chervin et al 1997). The MSLT is a state assessment and is thought to measure sleepiness on one occasion, in one situation, whereas the ESS is a trait assessment and measures recent sleepiness over the past month, in a number of different situations.

In this study, stronger significant relationships were found between the MWT and the ESS, compared to the MSLT. Perhaps closer relationships are found with the MWT

than the MSLT, because the ESS and MWT both measure the inability to stay awake, and not the ability to fall asleep. Both the MWT and the ESS are susceptible to similar levels of motivation, possibly making potential correlations stronger.

This potentially closer relationship between the MWT and the ESS is reflected in a number of other daytime measures that correlated more closely with the MWT than the MSLT. The MWT related to measures of well-being, depression, social life, physical ability, health transition and SAHS symptoms. Briones et al (1996) compared the MSLT with the SF-36 and only found the MSLT to correlate significantly, but weakly, to SF-36 vitality. In the current study, no such relationships were found between the MSLT or MWT and SF-36 vitality. The vitality dimension asks the following 4 questions - 'did you feel full of life? did you have a lot of energy? did you feel worn out? and did you feel tired?' These questions reflect a lack of energy and tiredness rather than actual sleepiness, and this may explain the lack of relationship with the MSLT and MWT in the current study.

The daytime variables that significantly correlated with the MWT estimated patients' SAHS symptoms, problems with work and home life, feelings of depression, factors affecting social activities, factors affecting physical ability and how health compares to one year ago. It may be that these variables are not necessarily the most severe decrements suffered by a patient, but that these are the ones that are easily recognised by the individual themselves. These significant variables are likely to be less subjective. For example, a physical functioning question such as 'Does your health limit you, climbing one flight of stairs?' is quite a straightforward question to assess. However, 'Do you feel full of life' is going to vary more between individuals, depending on their perception of the question. Referring back to Chapter 5, it was the similar daytime self-reports that related to nocturnal SAHS variables (section 5.4.2), except that significant relationships were found between nocturnal variables and SF-36 vitality scores.

6.4.3 Relationships between objective sleepiness and cognitive function measures

The MSLT did not significantly correlate with any tests of cognitive performance used in the current study. Similarly, Cheshire et al (1992) only found one significant relationship between MSLT and daytime tests, that being with IQ decrement ($r=0.46$, $p<0.05$). In contrast, the MWT significantly related to many measures of general cognitive functioning, sustained attention and reaction time.

As discussed above, the MWT may show stronger correlations with performance measures than the MSLT, because both the MWT and cognitive tests are susceptible to motivation and are measuring outcomes whilst trying to stay awake. Individuals that upgrade their performance on the cognitive function tests may be more likely to try hard to stay awake on the MWT.

In agreement with the study hypothesis, the MWT more closely relates to other measures of daytime function than the MSLT in the current SAHS population. It is possible that the MWT is the more appropriate test to perform in sleep apnoeics, or alternatively, the MWT is more similar to the other daytime function measures used here, therefore demonstrating stronger relationships.

6.4.4 General discussion

The MSLT is a widely used, well-validated test for measuring sleep tendency in patients with sleep disorders and for assessing the appearance of sleep onset REM periods for the diagnosis of narcolepsy. In addition, the MSLT aims to measure physiological sleep tendency by removing the majority of external environmental influences (Carskadon et al 1986), but this is not comparable with real life. The MWT on the other hand, measures the inability to stay awake and is influenced by greater motivational factors which may more closely relate to real life situations. Therefore the MWT may be the most appropriate test to use in SAHS patients, who tend to complain of their inability to stay awake rather than falling asleep too quickly when they try. The MWT may be more useful as a lab based test to quantify alertness ability

in SAHS patients, especially those who drive for a living or operate dangerous machinery (Poceta et al 1992).

Correlations with larger rho values were found with daytime interrelationships than between nocturnal and daytime measures. This may be because the daytime interrelationships are between tests performed on the same day, whereas nocturnal versus daytime relationships are comparing tests performed at night and on another day, which may demonstrate greater variation.

Even though correlations of a moderate size were found between the MWT and a whole range of daytime measures, relationships between both the MSLT and MWT and nocturnal SAHS measures were either weak or non-significant (Chapter 5). Alternative daytime function measures may improve relationships with nocturnal SAHS measures.

One recently devised measure is the Oxford Sleep Resistance (OSLER) Test (Bennett et al 1997). This is a simple behavioural test in which subjects have to press a button in response to a light emitting diode (LED) which is illuminated for 1 second in 3. When the subject does not respond for 21 seconds, the test is terminated on the assumption that the individual has fallen asleep. This is based on cross-validation work with the MWT (Bennett et al 1997). In the OSLER test validation, 10 normals and 10 severe SAHS patients (median oxygen saturation dip rate = 33) completed both the MWT and the OSLER test in a crossover design, on two separate occasions. Results demonstrated that both the MWT and the OSLER test could discriminate the SAHS patients from the normal controls. In addition, the mean values of the OSLER test and the MWT were not significantly different in either the patient or normal groups. The OSLER scores in the SAHS group tended to be longer compared to the MWT for each individual test, but were only significantly longer on the third test of the day in the SAHS group. These results imply that the OSLER test is slightly more stimulating than the MWT. However, this may not be to the OSLER test's disadvantage, as performing a simple task whilst trying to stay awake more closely

mimics real life. In addition, this non-EEG test will be terminated after 21 seconds even if an individual has failed to fall asleep in terms of R & K sleep, but may have in fact had a microsleep or a substantial lapse in concentration. Such phenomenon as these are still important, as they may occur at the wheel of a vehicle, for example. The validation work on this test does not suggest that the OSLER is likely to improve relationships with nocturnal SAHS measures, due to its similarity to the MWT. Although advantages of the OSLER test over the MWT are that it is less expensive, easier to perform than the MWT and requires less subjectivity. A large number study across the whole SAHS disease spectrum is required to further validate the OSLER test and examine correlations with nocturnal SAHS measures.

Ideally the best method of monitoring daytime sleepiness is using portable EEG equipment which can be worn in the workplace or in a vehicle, for the detection of microsleeps (Harrison & Horne 1996a). This is discussed further in Chapter 9.

6.4.5 Conclusion

The results presented suggest that the MWT rather than the MSLT may be a more useful tool in SAHS patients due to the relationships that exist between it and other important measures of daytime dysfunction. The relationships found are at most, moderate in size, and alternative measures of daytime sleepiness and performance may improve potential relationships.

Chapter 7

Patient Follow-up on Continuous Positive Airway Pressure (CPAP) Therapy

7.1 Introduction

Continuous positive airway pressure (CPAP) therapy (Sullivan et al 1981) is widely accepted as the treatment of choice for patients with SAHS, with evidence to suggest that CPAP improves daytime function (Engleman et al 1994a, 1998). This chapter describes follow-up data from the SAHS patients studied in Chapter 5, who were offered CPAP therapy.

The first aim of this chapter was to identify potential predictors of objective CPAP use from a diverse range of baseline nocturnal and daytime function measures, in an attempt to determine which patients are likely to use CPAP effectively and therefore gain therapeutic benefit.

The second aim of this chapter was to determine whether ESS scores consistently decreased after 12 months of CPAP therapy, and to examine the hypothesis that SAHS patients with high objective CPAP use demonstrate greater improvements in their level of subjective sleepiness. Additionally, the strength of baseline nocturnal predictors of improvements in ESS were examined.

Previous studies have attempted to identify baseline SAHS determinants of CPAP use. Reeves-Hoche et al (1994) and Engleman et al (1994b) found neither baseline AHI or BMI to predict objective CPAP use. The influence of the baseline arousal frequency and measures of hypoxaemia were not examined in either of these studies as potential predictors of CPAP use. Conversely, other studies (Meurice et al 1994, Pieters et al 1996, Krieger et al 1996) have found significant predictors of CPAP use. Meurice et al (1994) found the baseline AHI, % SWS and % stage 1 sleep to predict objective CPAP use (all $p > 0.29$, $p < 0.05$). Krieger et al (1996) sought determinants of

long-term objective CPAP use (mean follow-up of 1,176 days) on a large sample of 575 SAHS patients. Multiple regression analysis demonstrated that AHI and age independently contributed to the variance of CPAP use ($< 10\%$ of the variance), whereas baseline nap latency, subjective sleepiness and symptoms did not. Pieters et al (1996) found the nocturnal SAHS variable of movement arousal frequency to weakly predict objective CPAP use ($r=0.23$, $p<0.05$), but found no such relationships with BMI, apnoea frequency, % SWS and the oxygen desaturation index. These studies have found either weak coefficients (explaining less than 7% of the variance in mean CPAP use), or a lack of significant relationships between baseline SAHS predictors and mean objective CPAP use.

Significant improvements in ESS scores with CPAP therapy have previously been demonstrated (Johns 1992, Hardinge et al 1995, Smith & Shneerson 1995, Engleman et al 1996, 1998). The current study design improves on previous investigations by prospectively recruiting a large sample of consecutive patients, and recording objective CPAP use in all those recruited.

7.2 Methods

Patient recruitment and baseline SAHS measurements are described in Chapters 3 and 5.

7.2.1 Patients

Of the original 150 SAHS patients (Chapter 5), 137 were offered CPAP therapy by the clinicians for long term home use. The 13 patients who were not offered CPAP were significantly younger, with milder SAHS disease (Table 7.1). Non-CPAP patients were not significantly different from CPAP patients in terms of either subjective or objective measures of daytime sleepiness. Non-CPAP and CPAP patient group means were compared using a Mann-Whitney U test (Table 7.1).

Table 7.1; A comparison of CPAP and non-CPAP patients

Variable	CPAP group median (range) n=137	Non-CPAP group median (range) n=13	p value
Age	50 (22-71)	41 (33-62)	0.006
Arousal frequency	48 (8-141)	31 (16-54)	0.003
Apnoea + hypopnoea index	42 (8-144)	13 (7-21)	0.000
Epworth sleepiness scale	12 (0-24)	12 (1-17)	0.34
Multiple sleep latency test	9 (3-20)	12 (3-18)	0.89
Maintenance of wakefulness test	31 (3-40)	25 (13-40)	0.71

CPAP=Continuous positive airway pressure

7.2.2 Protocol

The 137 patients for whom long-term CPAP therapy was recommended returned to the sleep centre for a CPAP titration night. During this titration night, the lowest therapeutic CPAP pressure required to minimise respiratory events and arousals from sleep was established for each individual. Patients were then issued with a CPAP machine following the trial night, with the prescribed pressure set on an individual basis. All CPAP machines (Sullivan III or V, ResMed, San Diego, California) issued for subsequent home use contained time clocks. These time clocks display the total number of hours the CPAP unit has been run, allowing the objective mean machine ‘run time’ per night to be calculated for a given time period. CPAP run time data from all 137 patients was included in the analysis, which was performed on an intention to treat basis.

All CPAP patients were followed up with a phone call from a CPAP nurse at 2 weeks, and seen in the outpatient sleep clinic at 2 months and 1 year after commencing CPAP. If severe side effects occurred, a shorter interval between clinic visits was arranged. At clinic visits, CPAP use was noted, and CPAP machine and mask

problems or other adverse effects were discussed and rectified wherever possible by the nursing and medical sleep staff.

At 12 months after commencing CPAP therapy, all patients who were still in possession of a CPAP machine, regardless of CPAP use, were posted an Epworth sleepiness scale (ESS) for completion (3.4.1), enquiring about patient's recent dozing habits on CPAP therapy.

7.2.3 Statistics

The Δ ESS ([Baseline ESS] - [on CPAP ESS]) was normally distributed and compared to zero using a 2-tailed paired t-test. All other statistical analyses used non-parametric tests for non-normally distributed data. Between patient group comparisons were tested using the Mann-Whitney U test. Relationships between nocturnal SAHS measures and CPAP use and improvements in ESS (Δ ESS) were evaluated by Spearman rank correlations. Correlations were partial, controlling for age and awake oxygen saturation (section 5.2.4). Multiple regression analysis on ranked variables was used to identify independent predictors when an outcome measure significantly correlated with more than one variable. Age and awake oxygen saturation were forced into the multiple regression analysis prior to stepwise regression of the significant correlates. A two-tailed probability value of less than 0.05 was accepted as statistically significant. All data were analysed using SPSS for Windows 6.1. The statistically significant results in this chapter are presented in the tables in bold type for clarity.

7.3 Results

7.3.1 CPAP Use

Mean \pm SD CPAP run time in the 137 patients was 4.1 \pm 2.6 hours per night over the 12 months study period. Forty-nine (36%) patients used their CPAP machines for an average of less than 3 hours per night.

7.3.2 CPAP returnees

During the 12 month follow up period, 24 CPAP machines (18%) were returned to the sleep centre. A variety of reasons were given for returning CPAP units including: lack of benefit from CPAP (n=4); noise from the CPAP unit (n=4); bloating/flatulence (n=1); inability to cope with the CPAP pressure (n=3); CPAP mask problems (n=3); greater sleep disturbance on CPAP (n=1); referral for nasal surgery (n=1), patient death (n=1; of lung cancer); no reason given (n=6).

The 24 CPAP returnees did not significantly differ from those patients still on CPAP therapy in terms of age, AHI, arousal frequency, ESS, MSLT or MWT. However, significant differences in CPAP use at 2 months were found. Patients continuing on CPAP (median and range): 5.1 (0.1-9.0) hours per night; CPAP returnees: 0.6 (0-8.4) hours per night, $p < 0.00001$.

7.3.3 Baseline SAHS predictors of CPAP use

Relationships between baseline SAHS measures and mean CPAP use were examined to investigate whether predictors of CPAP use could be identified for the 137 patients issued with CPAP units. A few significant, but weak, correlations were found (Table 7.2; Figure 7.1). No significant relationships were found between mean CPAP use and baseline arousal frequency (Figure 7.2) nor with any other measure of sleep continuity, objective sleepiness or cognitive function.

Stepwise multiple regression analysis was then performed on the ranked baseline variables that significantly related to mean CPAP use. This analysis found the best predictors of mean CPAP use to be the AHI and the Stanford sleepiness scale (together explaining 26% of the variance in mean CPAP use).

Table 7.2; Spearman rank correlation matrix of the statistically significant relationships between baseline SAHS measures and mean objective CPAP use. All correlations are controlled for age and awake oxygen saturation.

Baseline SAHS Variable	Mean CPAP Use (hrs/night)
Apnoea+hypopnoea index	0.19*
2% desaturations	0.19*
3% desaturations	0.20*
4% desaturations	0.19*
Body mass index (kg/m ²)	0.23*
Collar size (cm)	0.25*
Waist circumference (cm)	0.24*
Nottingham health profile (part 2)	0.20*
Stanford sleepiness scale	0.19*
SF-36 vitality	-0.19*

SAHS=Sleep apnoea/hypopnoea syndrome; CPAP=Continuous positive airway pressure; *p<0.05

Figure 7.1; Scatterplot of the relationship between AHI and objective CPAP run time ($\rho=0.19$, $p=0.03$)

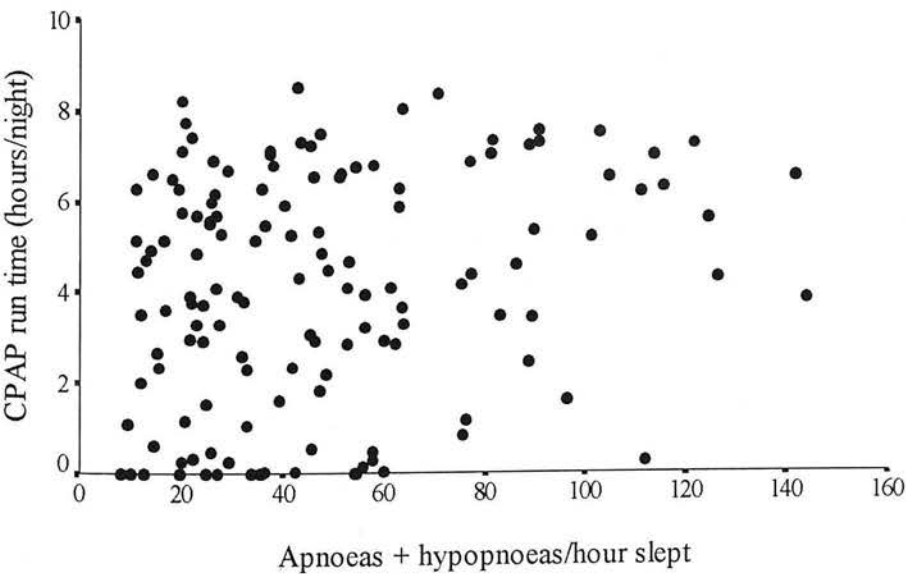
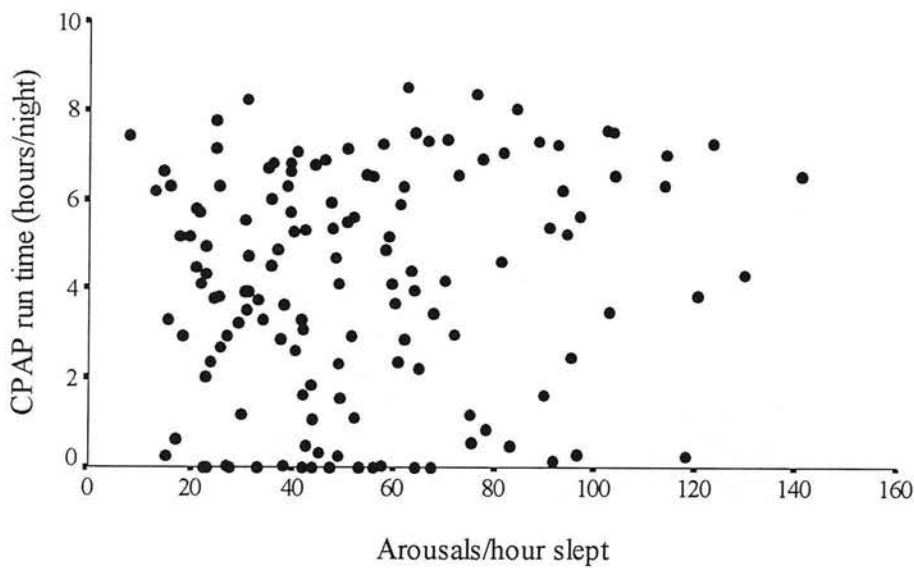


Figure 7.2; Scatterplot of the relationship between arousals and objective CPAP run time ($\rho=0.09$, $p=0.28$)

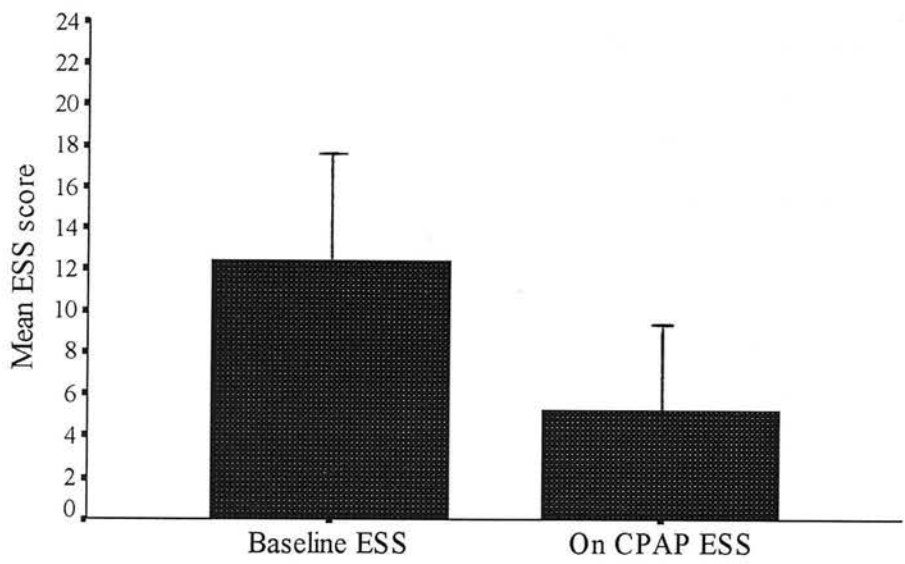


7.3.4 Improvements in ESS with CPAP therapy

ESS questionnaires were sent to the 113 patients still in possession of a CPAP machine at 12 months follow up. Ninety-two patients returned their ESS questionnaires (81% response rate). The non-responders were not significantly different in terms of age, disease severity or sleepiness (all $p>0.19$). However, the non-responders did have a significantly lower CPAP use at 12 months (median and range): responders 5.6 (0.7-8.7) hours per night; non-responders 2.9 (0-6.6) hours per night; $p=0.0001$.

For the 92 responders, the ESS (mean \pm SD) significantly improved with CPAP therapy (Baseline ESS: 12 ± 5 , on-CPAP ESS: 5 ± 4 ; $p<0.0001$), (Figure 7.3).

Figure 7.3; Bar chart representing baseline and on-CPAP mean (SD) ESS scores in 92 SAHS patients.



7.3.5 Relationships between nocturnal SAHS measures, mean CPAP use and improvements in ESS

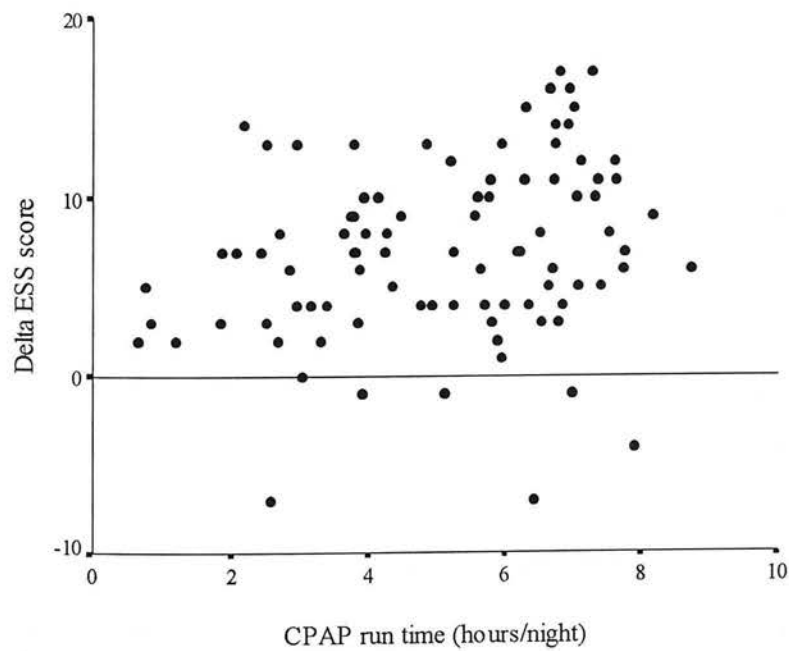
Improvements in the ESS score from baseline to on-CPAP (Δ ESS) provide a useful, though subjective, outcome measure of the benefit of CPAP therapy. Δ ESS was significantly related to measures of hypoxaemia, i.e. the greater the frequency of oxygen desaturations, the greater the improvements in ESS. However, Δ ESS was not significantly associated with arousal frequency or AHI (Table 7.3). A significant relationship between Δ ESS and mean CPAP use was also found (Table 7.3; Figure 7.4), linking greater improvement in ESS score with higher CPAP use.

Table 7.3; Spearman rank correlation matrix of relationships between baseline PSG measures, mean objective CPAP use and Δ ESS. All correlations are controlled for age and awake oxygen saturation.

	Δ Epworth sleepiness scale score
Arousal frequency	0.13
Apnoea+hypopnoea index	0.08
2% desaturations	0.18
3% desaturations	0.21*
4% desaturations	0.22*
Minimum saturation	-0.28**
Mean CPAP use	0.30**

Δ ESS=[Baseline mean ESS score - mean ESS score after 12 months on CPAP]; CPAP=Continuous positive airway pressure; * $p<0.05$; ** $p<0.01$

Figure 7.4; Scatterplot of mean CPAP run time versus Δ ESS (Baseline mean ESS - on CPAP ESS), $\rho=0.30$, $p=0.004^*$



* The points above the horizontal line represent improvements in ESS with CPAP therapy, those below the horizontal line represent worsening of ESS score with CPAP therapy.

Stepwise multiple regression analysis was then performed on the baseline PSG measures and mean CPAP use which significantly related to Δ ESS. The analysis found the best independent predictors of Δ ESS to be the mean CPAP use and the minimum oxygen saturation (together explaining 13% of the variance in Δ ESS).

7.4 Discussion

7.4.1 Baseline SAHS predictors of CPAP use

There were only a few significant baseline predictors of CPAP use, including the AHI and oxygen desaturation measures. Each explained less than 7% of the total variance in CPAP use. These relationships are compatible with previous studies which found either weak predictors of objective CPAP use (Meurice et al 1994, Pieters et al 1996, Krieger et al 1996) or a lack of predictors of objective CPAP use (Kribbs et al 1993, Reeves-Hoche et al 1994, Engleman et al 1994b).

The current study improved on previous studies (Kribbs et al 1993, Meurice et al 1994, Engleman et al 1994b, Reeves-Hoche et al 1994, Pieters et al 1996) by using a larger sample size of 137 patients. In addition, the current study measured a more diverse range of possible baseline SAHS predictors. These included nocturnal measures of sleep fragmentation and sleep continuity, and daytime measures of subjective and objective sleepiness, cognitive function and psychopathology. Previous studies (Kribbs et al 1993, Meurice et al 1994, Engleman et al 1994b, Reeves-Hoche et al 1994, Pieters et al 1996, Krieger et al 1996) only presented data on the predicting effects of the following: AHI, movement arousal frequency, minimum oxygen saturation, % stages 1 & 2 sleep and SWS, BMI, age, MSLT and years of education. Despite the wide range of possible predictors of CPAP run-time in the current study, in the correlational analysis few significant variables were identified. In the multiple regression analysis, the AHI and SSS scores were the best baseline predictors of mean CPAP use.

The weak relationships found between baseline SAHS measures and objective CPAP use are likely to be due to inter-patient variability (section 5.4.4). For example, some patients like, and others detest, the concept of sleeping with CPAP. In addition, some patients may require all night CPAP use to gain therapeutic benefit, whereas others may only require CPAP therapy for part of the night. Engleman et al (1994a) have demonstrated that improvements in daytime function are found with a low mean CPAP use of 3.4 hours per night. Therefore, if patients demonstrate variability in their CPAP use required to gain the same benefit, regardless of initial disease severity, baseline predictors of CPAP use are likely to be weak.

7.4.2 Relationships with improvements in daytime function

Examining baseline predictors of CPAP use has demonstrated that poor relationships exist, possibly due to patients' variation in perceived benefit for a given use. By examining improvements in baseline measures with CPAP, in particular symptoms perceived by the patient, the therapeutic effect of CPAP can be studied.

Time was not available in this project to perform repeat daytime testing in all 137 CPAP patients. However, as part of another study in the sleep centre, 62 of the current CPAP patient population were followed up with repeat daytime tests after 6 months of CPAP therapy. Not all 137 CPAP patients were followed up, as this second study commenced part way through the current study. I performed the baseline daytime tests, and the second post-CPAP assessment was performed by two colleagues. These results are not presented in detail in this thesis, but do merit discussion. Significant treatment related improvements in sleep latency on the MWT were found, as was previously demonstrated by Sangal et al (1992b). Improvements were also observed in subjective sleepiness, well-being, quality of life and symptoms with CPAP. These results are in agreement with previous studies that have also demonstrated improvements in ESS (Johns 1992, Smith & Shneerson 1995, Hardinge et al 1995, Engleman et al 1998), SF-36 dimensions (Smith & Shneerson 1995, Jenkinson et al 1997), mood (Engleman et al 1994a) and SAHS symptoms (Engleman et al 1994a, 1998). Improvements in cognitive performance scores measuring

visuomotor coordination, information processing, attention and general cognition were also found after 6 months of CPAP therapy. Familiarisation with the cognitive tests was not performed and so improvements found here are likely to be influenced by learning effects (Engleman et al 1994a).

Baseline sleep study variables were correlated with the change in daytime function measures (Δ =delta values) after 6 months on CPAP therapy. The arousal frequency only predicted one outcome measure, Δ reaction time gaps, and AHI only significantly correlated with Δ digit symbol. Hypoxaemia variables predicted a range of improvements in daytime function including MWT, SF-36 measures and trail making A. These results are in broad agreement with previous studies (Sangal et al 1992b, Engleman et al 1994a), in that CPAP therapy improves daytime function. This study suggests that these improvements in daytime function occur independently of baseline disease severity as measured by AHI and arousal frequency, and only a few improvements in daytime function significantly relate to baseline hypoxaemic variables.

7.4.3 Improvements in ESS with CPAP

This study has also demonstrated that ESS scores significantly decrease after 12 months of CPAP therapy in a consecutive sample of 92 SAHS patients. The mean ESS score on CPAP decreased to levels consistent with a middle-aged working community sample of normal subjects (Johns & Hocking 1997). This study confirms and extends the results of previous studies based on smaller samples of SAHS patients (Johns 1992, Smith & Shneerson 1995, Engleman et al 1998) and studies which did not measure objective CPAP run time in all patients (Johns 1992, Hardinge et al 1995, Engleman et al 1996).

It is possible that this study and other uncontrolled studies (Johns 1992, Hardinge et al 1995, Smith & Shneerson 1995, Engleman et al 1996) found decreases in ESS scores with CPAP therapy as a result of placebo effects and cognitive dissonance-type effects. For example, administering a treatment of any type may

improve symptoms, both in terms of subjective benefit, and even when no benefit is found, the fact that there 'ought to be a treatment benefit' may improve scores. In addition, pleasing the experimenter may also create subjective improvements in symptoms with therapy. Engleman et al (1998) performed a small number, randomised, single blind, placebo controlled crossover study, and found ESS scores to significantly decrease with CPAP therapy compared to a placebo tablet. However, as the current study was uncontrolled, it can only be speculated that the improvements found in ESS were due to the therapeutic effects of CPAP.

The positive relationship between mean CPAP use and Δ ESS, supports the hypothesis that the decrease in ESS with CPAP is due to the therapeutic effect of CPAP, i.e. the more an individual uses their CPAP machine, the greater the improvement in subjective sleepiness, or the greater the improvement in subjective sleepiness, the greater the CPAP use.

Baseline nocturnal predictors of improvements in ESS were also examined in this study. Δ ESS significantly, but weakly, correlated with measures of hypoxaemia alone. In contrast, a preliminary report by Bennett et al (1998) found significant relationships between Δ ESS and AHI and measures of sleep fragmentation (frequencies of microarousals, movement arousals, autonomic arousals and changes in neural net EEG), all $r > -0.38$, $p < 0.05$. The difference between the current results and those of Bennett et al (1998) are difficult to explain. There were differences in the demographics of the populations studied. Bennett et al (1998) examined relationships in 41 patients, including a greater proportion of mild patients and also normal subjects (median AHI=18, range 0-123), whereas in the current study the demographics of the 92 patients with Δ ESS data had a median AHI of 44 and a range of 11-144. It is possible that the normal subjects included in the analysis by Bennett et al (1998) increased the likelihood of significant correlations, by providing data points with low levels of sleepiness and sleep fragmentation. In the current study it is possible that relationships with Δ ESS were only found with hypoxaemia, because measures of hypoxaemia are more robust than EEG scored indices of sleep fragmentation.

Significant relationships could be influenced by variability in signal and scoring reliability rather than a direct physiological effect (see 5.4.4). It is interesting to note that Bennett et al (1998) found the best predictors of Δ ESS to be digitally-determined body movement events, and computer based neural network EEG analysis, together explaining 51% of the variance. Thus their use of different variables may contribute to the discrepancies with the current study - nevertheless, in their study AHI was significantly ($r = -0.53$, $p < 0.001$) correlated with Δ ESS, but there was no such significant relationship in the current study.

In summary, the ESS is a useful assessor of response to CPAP therapy. However, one criticism of postal questionnaire studies is the potential selection bias that is created by the subset of non-responders. In this study, the non-responders were significantly poorer CPAP compliers, exactly the group of individuals a follow-up questionnaire is aiming to target. Hence, if a patient scores highly on their follow-up ESS (>10), or fails to return their questionnaire, they are more likely to have a poor CPAP use and require an interim clinic appointment to discuss CPAP problems and be challenged about poor CPAP use. Administering the ESS on-CPAP therapy, as part of routine follow up, is simple and cheap to perform and would be easy to implement. The ESS is a subjective, retrospective measurement. However, it represents the perceived state of the patient, who will self-determine their CPAP use depending on their self-assessed therapeutic benefit.

7.4.4 Conclusion

In conclusion, this chapter has demonstrated that CPAP therapy reduces the ESS score to normal levels. However, prospectively determining who will use their CPAP machine and gain therapeutic benefit is difficult to predict. If finances allow, perhaps all patients with sleep disordered breathing should be offered a trial of CPAP. Ultimately, regardless of disease severity, the patient determines whether they will use their CPAP unit. This depends on personal, and to some extent, spouse benefit.

Chapter 8

Is in-lab polysomnography required prior to measuring objective sleepiness?

8.1 Introduction

Guidelines for performing the multiple sleep latency test (MSLT) were produced in 1986 by Carskadon and co-workers. They recommend that the MSLT is performed on a day following clinical polysomnography (PSG) to provide “accurate documentation of the preceding night’s sleep”. This standard procedure has also been followed by Poceta et al (1992) using the maintenance of wakefulness test (MWT). Documentation of the preceding night’s sleep can be measured using ambulatory PSG equipment in the patient’s own home, or more commonly, in the sleep laboratory.

The correlational study performed on 150 SAHS patients (Chapter 5), did not follow these standard MSLT guidelines, as both the MSLT and MWT were performed after a normal night’s sleep at home. There were three reasons for this; firstly, to measure the daytime sleepiness that occurs after a normal night’s sleep at home, rather than after a PSG interfered night, secondly, to follow the same protocol as the previous small correlational study performed in the lab (Cheshire et al 1992), and thirdly to limit costs. The current study found a high mean MSLT nap latency of 9.7 minutes and our group previously reported a median MSLT sleep latency of 10 minutes (Cheshire et al 1992). These MSLT values are high compared to other studies in sleep apnoeics (Roth et al 1980, Guilleminault et al 1988b, Roehrs et al 1989) where full diagnostic polysomnography was recorded in the sleep lab on the night prior to the MSLT.

The aim of the current study was to compare objective daytime sleepiness recorded after a night’s sleep at home, with minimal neurophysiological sleep recording equipment, versus full diagnostic in-laboratory PSG. The hypothesis was that SAHS patients are sleepier (as measured by the MSLT and MWT) after a PSG night in the

sleep centre, than after a night at home with less instrumentation. A secondary aim of the study was to compare sleep quality and sleep fragmentation when recorded at home versus in the sleep centre.

No previous studies have compared objective daytime sleepiness after nights in the lab and at home in sleep apnoeics. One study (Edinger et al 1997a) has compared objective daytime sleepiness between 32 older insomniacs and 32 age and gender-matched normal controls after a night in the sleep lab or at home. All subjects underwent 3 consecutive nights of in-lab monitoring of sleep parameters, and 3 consecutive nights of identical in-home monitoring in a crossover design. The MSLT was only performed on day 4 of the first study limb. The combined results of the insomniacs and normal subjects found no significant differences in sleepiness as measured by the MSLT after lab versus home recorded nights (Edinger et al 1997a).

Sewitch & Kupfer (1985) compared neurophysiological sleep parameters measured in the sleep lab versus at home in a group of normal subjects, and found no significant differences in sleep parameters. Edinger et al (1997b) also measured lab and home based PSG in normal subjects and insomniacs, but did not compare nocturnal data between the two situations. Instead, this study focused on the differences in sleep parameters between normal controls and insomniacs within the two different recording locations.

Studies have examined relationships between nocturnal SAHS variables measured using limited screening devices in the home and in-lab PSG in sleep apnoeics. Results demonstrate reproducible SAHS severity indices at home in line with lab based PSG (Ancoli-Israel et al 1981, Redline et al 1991, White et al 1995, Whittle et al 1997b, Parra et al 1997). To my knowledge no such studies in sleep apnoeics have compared ambulatory PSG in-home versus that recorded in the lab.

8.2 Methods

8.2.1 Patients

Consecutive clinic patients suspected of having SAHS, who were attending the sleep centre for diagnostic in-lab polysomnography were approached to participate in the study. The entry and exclusion criteria are listed in Table 8.1.

Table 8.1; Recruitment Criteria

<p>Inclusion Criteria</p> <ul style="list-style-type: none">• Living within Edinburgh city boundary• Aged 18-75• Self-reported symptoms of either sleepiness (ESS≥8) or 2 other major symptoms of SAHS <p>Exclusion Criteria</p> <ul style="list-style-type: none">• Coexisting causes of daytime sleepiness (e.g. shift workers)• Self-reported features of other sleep disorders• Major psychiatric and neurological disorders• Coexisting causes of hypoxaemia (e.g. COPD, nocturnal asthma)
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Twenty-one patients were eligible for the study and 13 (12 men) agreed to participate. The 8 declined because of work pressures (n=5) or family commitments (n=3). In addition, one patient failed to complete the study due to work commitments, leaving 12 consecutive patients who completed the study (Table 8.2).

Table 8.2; Patient demographics (n=12)

Measurement	mean (SD)	range
Age (years)	50 (13)	28 - 74
BMI (kg/m ²)	30 (6)	24 - 44
In-lab AHI (per hour slept)	34 (30)	7 - 97
Epworth sleepiness scale	12 (6)	3 - 22
Collar size (cm)	40 (3)	33 - 45
Waist size (cm)	100 (16)	77 - 136

BMI=Body mass index; AHI=Apnoea + hypopnoea index.

All patients self-reported symptoms of either sleepiness (ESS≥8) or 2 other major symptoms of SAHS (Whyte et al 1989). These symptom ratings were taken from the in-house sleep/wake questionnaire (Appendix B). The percentages of SAHS symptoms reported by patients are described in Table 8.3.

Table 8.3; Percentages of self-reported patient symptoms

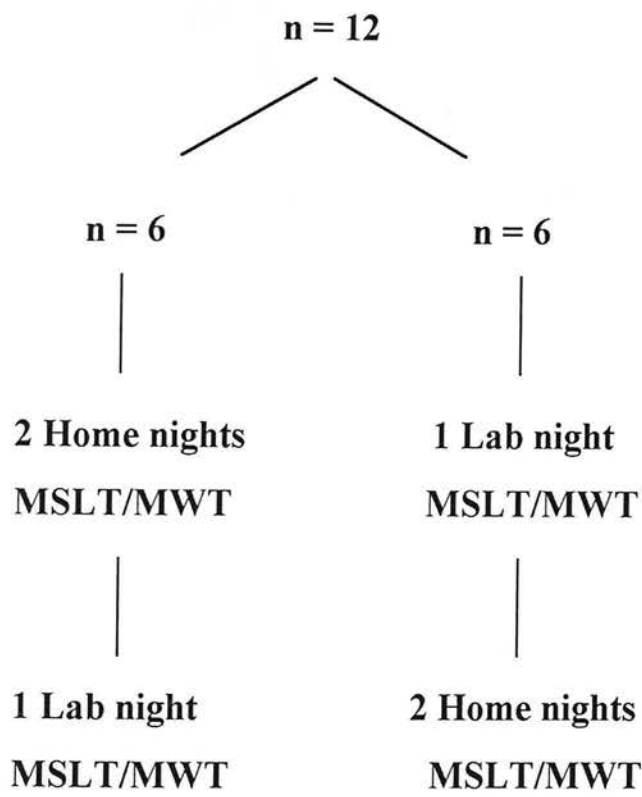
Self-reported symptoms*	% patients reporting symptom
Snoring	92%
Daytime sleepiness (ESS≥8)	83%
Unrefreshing sleep	58%
Witnessed breathing pauses	58%
Choking episodes	8%
Nocturia	8%

ESS=Epworth sleepiness scale; * All symptoms reported from our in-house sleep/wake questionnaire (Appendix B).

8.2.2 Protocol

Patients were randomised using balanced blocks to commence with either the home or lab study limb in a crossover design (Figure 8.1).

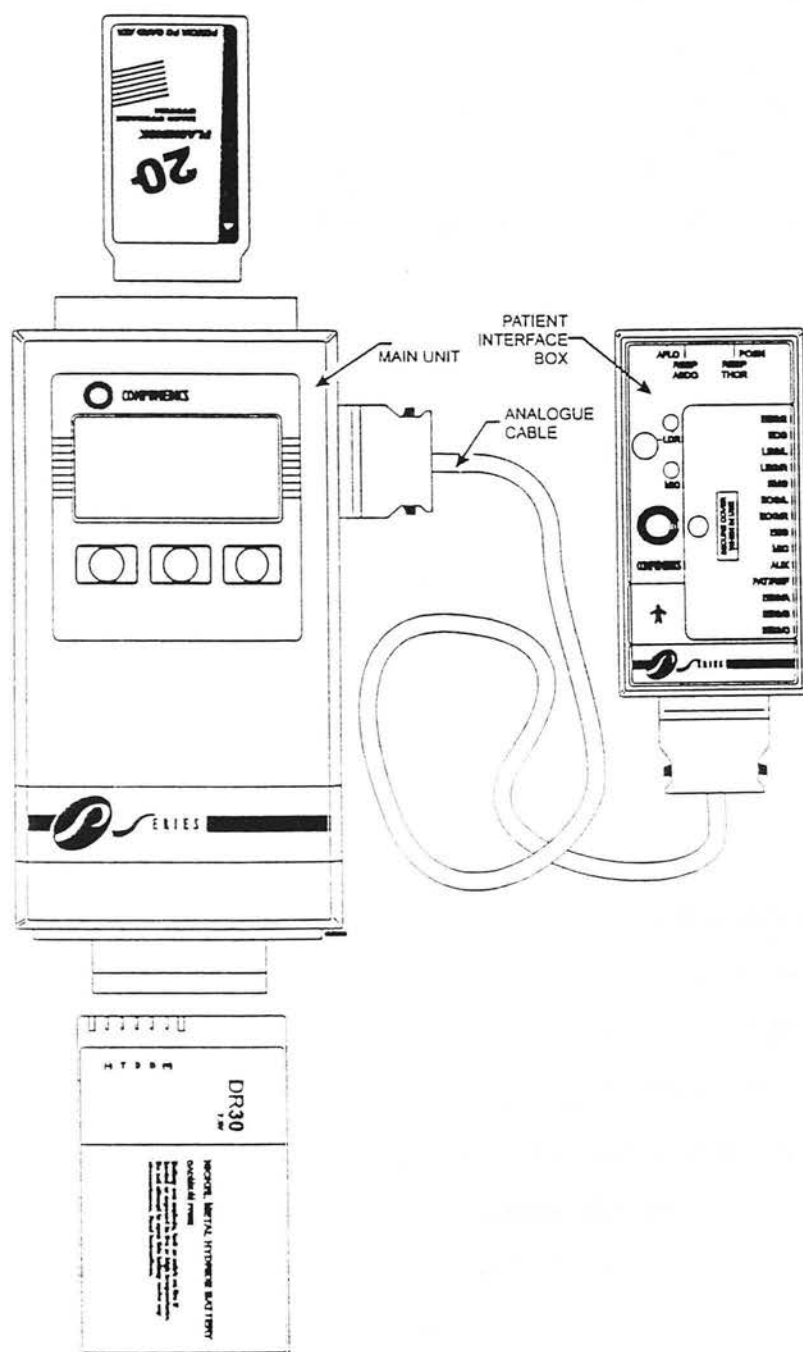
Figure 8.1; Study Design



In-home Study Limb

Sleep was recorded using a portable polysomnographic recording system (P-series 2, Compumedics S, Australia; Figure 8.2). As the prime intention was to determine whether lab PSG, the night before MSLT/MWT, changed the MSLT/MWT result compared to a normal night’s sleep at home, an acclimatisation night was included on the home limb. On this limb only neurophysiological sleep quality was recorded and not respiratory and other signals. The procedure for the acclimatisation and study nights was the same.

Figure 8.2; Portable polysomnographic recording system*



* Reprinted with permission of Compumedics S, Australia

I arrived at the patient's home at a prearranged time to attach the sleep monitoring equipment. This was 2 hours before the patient's usual bedtime, to allow 1 hour for the equipment to be attached, and 1 hour for the patient to relax and familiarise themselves with the equipment. Instructions to the patient regarding the avoidance of alcohol and caffeine on the evening of the studies had been previously discussed. All patients were wired up with scalp electrodes to record submental EMG, right and left outer canthus EOG - referenced to Fpz, bipolar EEG from sites Cz/Pz, and additionally from C3/C4 as a back up EEG signal, and a reference electrode at A2 (Cooper et al 1980). Following the lab protocol, EEG electrodes were secured using collodion, and all other electrodes were secured with adhesive tape. All electrodes were connected to a patient interface box (PIB), which clipped to the patient's pyjama waistband. The PIB was attached by a 2 metre analogue cable to the main portable unit (Figure 8.2). The main portable unit contained a 20MB memory card for data storage, and a 7.2V Nickel Metal Hydride battery to power the whole system, thus making it ambulatory. All neurophysiological channels were viewed to check technical signal quality on-line from the main portable unit. Impedances were measured and adjusted to less than 5 kOhms.

Patients were instructed to go to bed at their usual time. Recording was commenced by myself before leaving the house. Patients were instructed to note down (from the clock on the main portable unit) their 'lights-out' time in their sleep diary (Appendix C). Patients were then left unattended until the morning. I arrived back in the morning at a time prearranged to suit the patient. Patients completed their sleep diaries, noting down the time of their final awakening in the morning, and whether the sleep was representative of a normal night for them (Appendix C). All equipment was removed and returned to the lab. The same procedure was repeated the following (study) night and morning. On the second morning, patients attended the lab for their daytime assessments. All patients lived within 20 minutes of the sleep centre, and so could comfortably arrive in the sleep centre by 9.15 am.

In-Lab Study Limb

Patients arrived at the sleep centre between 9.00 and 9.30 pm and were wired up for full diagnostic polysomnography as described in section 3.1. In addition to the scalp electrodes attached on the home limb, patients also had an oximeter, airflow monitor, abdominal and thoracic plethysmography bands, a position monitor, leg EMG electrodes and ECG leads attached. 'Lights out' was standardised to between 10.45 and 11.15 pm. In the morning patients were awakened at 7.00 am and all sensors removed except for the sleep monitoring electrodes. Patients remained in the lab for their daytime assessments.

Daytime Assessments

Objective daytime sleepiness was measured across the day by the MSLT (at 10.00, 12.00, 14.00 & 16.00) and the MWT (at 11.00, 13.00, 15.00 & 17.00) as described in section 3.4.2. In addition, height, weight, collar size and waist size were measured, along with a background questionnaire to record medication, past medical history, tobacco and alcohol intake, occupation and educational status.

8.2.3 Off line data analysis

The overnight sleep data recorded from the portable home studies was downloaded from the memory card onto the Compumedics PC system for subsequent analysis. Home study data was analysed from 'lights-out' to the final awakening, the times of which were subjectively recorded by the patient in their sleep diaries (Appendix C). Data acquired prior to 'lights-out' were discarded. All polysomnography records and MSLT/MWT from lab and home limbs were scored according to the standard lab criteria described in Chapter 3.

8.2.4 Statistics

Sleep parameters and MSLT/MWT data were analysed using two-way analysis of variance (ANOVA) for repeated measures, with order of location as a between subject factor, and home versus lab location as a within subject factor. No order

effects were found between the home and lab limbs. A probability value of less than 0.05 was accepted as statistically significant. Data were analysed using SPSS for Windows 6.1. The statistically significant results in this Chapter are presented in the tables in bold type for clarity.

8.3 Results

8.3.1 Home versus lab objective daytime sleepiness

There were no significant differences in objective daytime sleepiness, as measured by both the MSLT and MWT, after a night in the sleep lab versus a night at home (Table 8.4, Figures 8.3 & 8.4). There were also no significant differences between individual MSLT and MWT daytime naps measured after lab versus home limbs (Table 8.4).

Table 8.4; Comparisons between in-home and in-lab objective daytime sleepiness

Daytime nap variable	After home study mean (SD)	After lab study mean (SD)	p value
10.00 MSLT (mins)	13.0 (5.1)	10.8 (5.2)	0.35
12.00 MSLT (mins)	10.3 (6.1)	12.7 (6.7)	0.13
14.00 MSLT (mins)	9.5 (5.9)	11.5 (5.9)	0.28
16.00 MSLT (mins)	10.8 (6.6)	10.6 (5.0)	0.93
11.00 MWT (mins)	31.5 (10.1)	29.8 (8.8)	0.64
13.00 MWT (mins)	29.1 (13.4)	28.5 (11.9)	0.85
15.00 MWT (mins)	29.2 (12.1)	26.4 (12.7)	0.23
17.00 MWT (mins)	33.5 (10.6)	31.8 (11.5)	0.67
Mean MSLT (mins)	10.9 (4.7)	11.4 (4.7)	0.31
Mean MWT (mins)	30.8 (9.3)	29.1 (9.5)	0.26

MSLT=Multiple sleep latency test; MWT=Maintenance of wakefulness test

Figure 8.3; Bland & Altman plot of relationships between in-lab and in-home mean MSLT scores

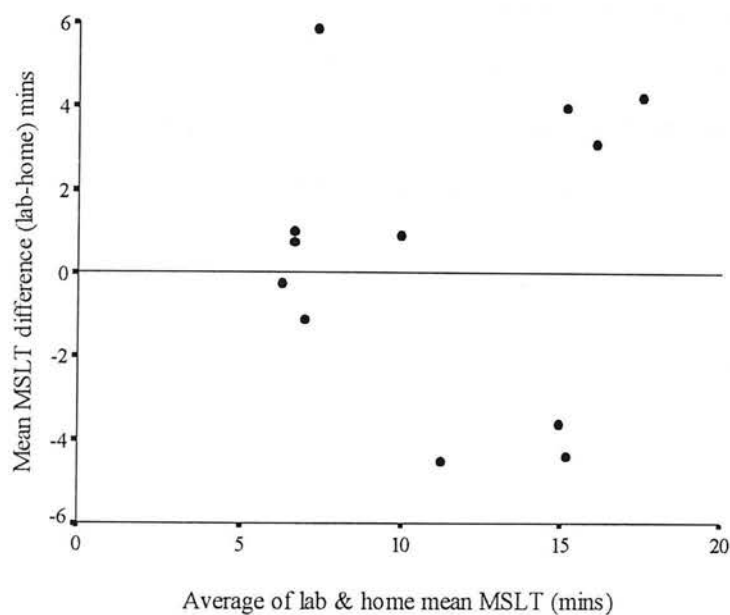
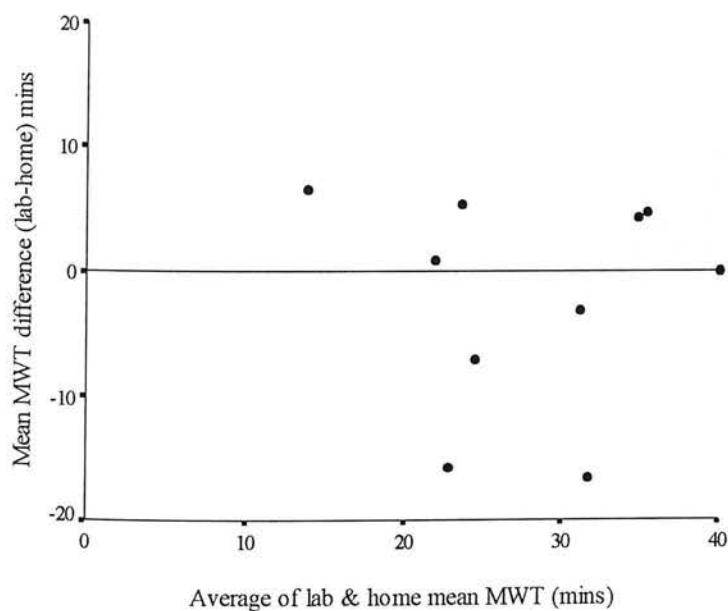


Figure 8.4; Bland & Altman plot of relationships between in-lab and in-home mean MWT scores*



* The right-most data point represents 3 overlying points

8.3.2 Comparison of home versus lab recorded sleep variables

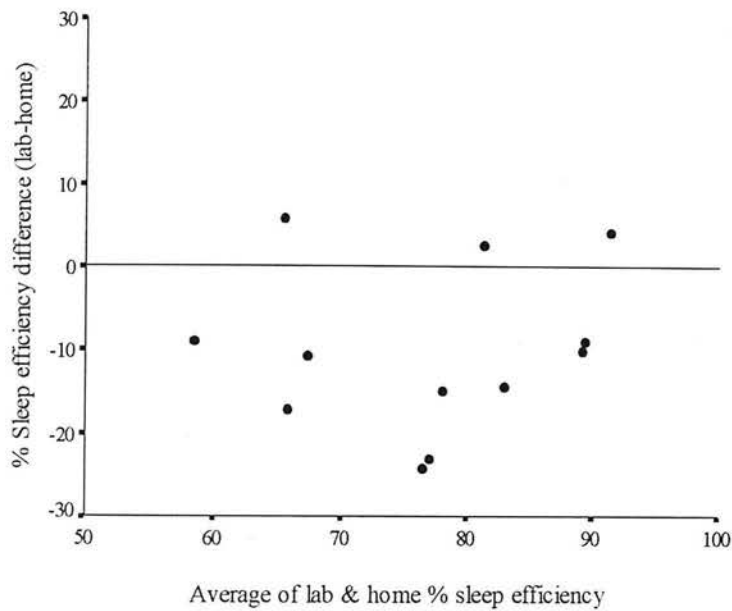
Patients spent significantly less time in bed (TIB) at home than in the lab, yet did not differ in total sleep time (TST). Therefore, at home, patients had a significantly higher sleep efficiency (Table 8.5, Figure 8.5). Patients also had significantly fewer arousals from sleep at home compared to in the lab (Table 8.5, Figure 8.6). At home, significantly greater percentages of REM sleep and slow wave sleep (Figure 8.7), and a lower percentage time spent awake were found (Table 8.5).

Table 8.5; Comparisons between home and in-lab nocturnal sleep variables

Measurement	Home study mean (SD)	Lab study mean (SD)	p value
Arousal frequency /hr slept	31 (14)	53 (26)	0.004
TIB (mins)	448 (46)	481 (17)	0.04
TST (mins)	365 (53)	345 (57)	0.21
% sleep efficiency	82 (11)	72 (12)	0.007
SOL (mins)	17 (17)	16 (11)	0.77
% wake	14 (9)	25 (12)	0.007
% stage 1 sleep	6 (3)	5 (3)	0.37
% stage 2 sleep	43 (7)	45 (10)	0.52
% slow wave sleep	16 (6)	10 (5)	0.003
% REM sleep	20 (7)	15 (6)	0.003

TIB=Time in bed; TST=Total sleep time; SOL=Sleep onset latency; REM=Rapid eye movement sleep;

Figure 8.5; Bland & Altman plot of relationships between in-lab and in-home % sleep efficiency*



* Sleep efficiency = (total sleep time/time in bed)x100

Figure 8.6; Bland & Altman plot of relationships between in-lab and in-home arousal frequencies

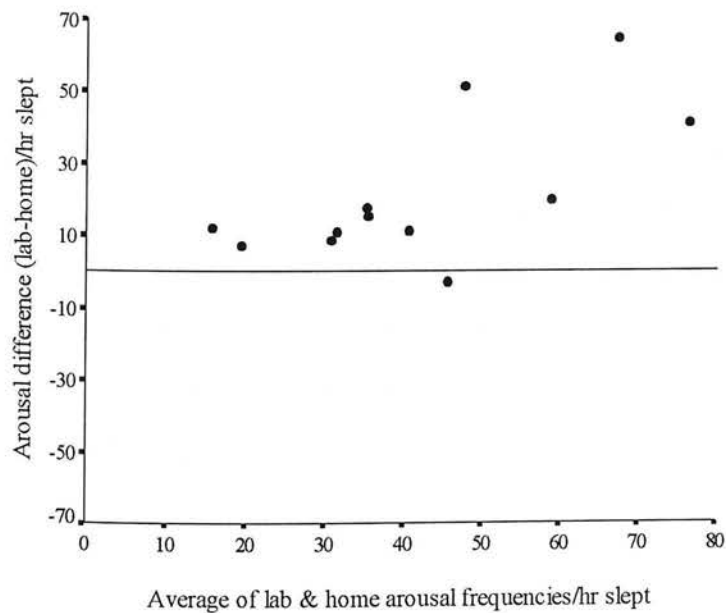
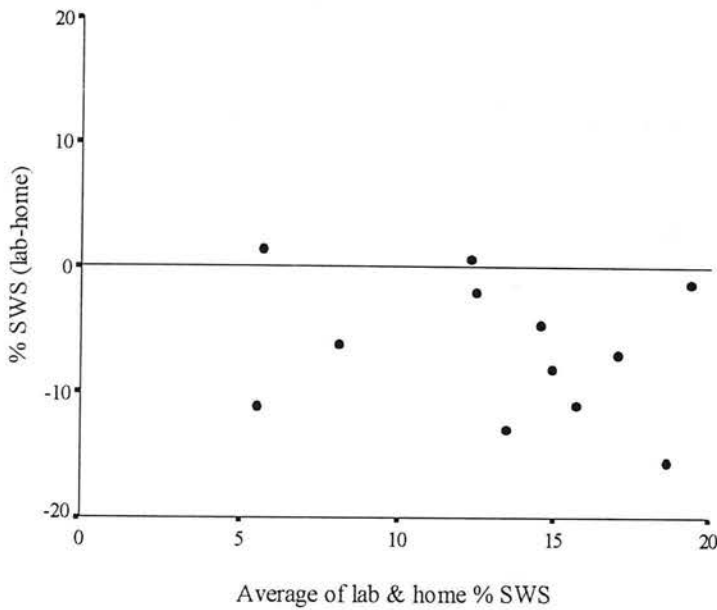


Figure 8.7; Bland & Altman plot of relationships between in-lab and in-home % slow wave sleep (SWS)



8.4 Discussion

This study presents preliminary findings that daytime sleepiness, as measured by the MSLT and MWT, is not significantly different following a night of PSG in the lab versus a night with limited instrumentation at home. These results are in agreement with a larger study (n=64) in insomniacs and normal controls (Edinger et al 1997a). The current findings also demonstrated that, on the home limb, a significantly better quality of sleep was found, in terms of a higher sleep efficiency, more SWS and REM sleep and less arousals from sleep. These results contrast with the study by Sewitch & Kupfer (1985) who found no significant differences in sleep variables when comparing home and lab recordings. However, Sewitch and Kupfer (1985) studied sleep patterns

in 24 normal healthy controls and performed acclimatisation nights on both the home and lab limbs.

8.4.1 MSLT and MWT scores

The results presented here suggest that the mean MSLT and MWT sleep onset latencies are the same despite the differences found in the prior night's sleep. The Bland & Altman plots (Figures 8.3 & 8.4) demonstrate individual differences in the MSLT and MWT mean scores for each patient, with some patients sleepier after a night at home, and others sleepier after a night in the lab, thus making the overall differences in location of prior night's sleep non-significant. This study does not support the hypothesis that patients are sleepier after a night in the lab compared to home, rather it suggests that location of prior night's sleep has no effect on objective daytime sleepiness. This suggests that the high mean MSLT value observed in Chapter 5 is not likely to result from performing the MSLT/MWT after a night's sleep at home. Perhaps the sleep disruption recorded on the home night, using the limited equipment, is far greater than the 'normal' level of sleep disturbance on a night at home with no intervention whatsoever. The current study cannot answer this question. Ideally, a three-way crossover study would have been performed, with the MSLT and MWT recorded after (1) PSG night in the lab, (2) PSG night at home and (3) normal night's sleep at home, thus comparing the effect of the limited home equipment with no intervention in familiar surroundings. This protocol was not undertaken, as it was too demanding for the patient. The fact that mean MSLT and MWTs are not significantly different after lab or home nights does not prove that it is pointless monitoring sleep the night before MSLT/MWT. It remains possible that the occasional individual will deliberately restrict their nocturnal sleep if unmonitored at home in order to produce spurious evidence of excessive daytime sleepiness. It remains to be determined whether this is a common phenomenon.

8.4.2 Home versus lab sleep parameters

A significantly better quality of sleep was found on the home limb compared to the lab limb, in terms of less sleep fragmentation and deeper sleep. In all but one patient, the arousal frequency was greater on the sleep lab night than the home night. Although numbers are small, it appears that there were greater discrepancies between home and lab arousal frequencies at the more severe end of the disease spectrum (Figure 8.6). The current data cannot identify the cause of better sleep quality at home, but various reasons can be speculated upon.

- Recording sleep in the home occurs in surroundings familiar to the patient, which could decrease anxiety. Patients can follow their normal bedtime routine, and choose the bedtime to suit them, depending on their level of sleepiness. This was reflected in the significantly shorter time spent in bed at home. Interestingly, despite this shorter time in bed, the same mean quantity of sleep was recorded as on the lab limb. Thus patients at home have a higher sleep efficiency. It is likely that at home, patients only retire to bed when they are feeling sleepy and arise when refreshed and are more efficient in utilising their time in bed. In the lab, 'lights out' and wake up times are standardised so patients may wake up prior to the standardised wake up time, decreasing sleep efficiency.
- In the home, patients were given an acclimatisation night to provide familiarisation of the equipment. An acclimatisation night was not performed on the lab limb, as this is not standard lab practice, therefore the lab equipment may appear more obtrusive to the patient.
- In the home, the instrumentation was minimal, consisting of 10 scalp electrodes positioned away from the face and securely attached to the patient interface box, with one single connecting lead to the main patient unit (Figure 8.2). In the sleep lab, in addition to the electrodes, the following sensors are also attached: airflow monitor, pulse oximeter, 2 plethysmography bands, 2 leg EMG sensors, a position monitor and 2 ECG leads. These are all independently connected to the

patient headbox, so in effect there are leads coming from many sites on the body. This additional instrumentation is more likely to disturb an individual's sleep. The lab PSG equipment may also restrict the patient's body position in bed. It is anecdotally reported that patients in the sleep lab lie supine for a large proportion of the night. By lying supine, patients increase their likelihood of having breathing pauses, and thus sleep fragmentation. This alone may explain the increased sleep disruption in the lab compared to at home in a group of patients with SAHS.

- The presence of a video camera and an observing nurse/technician during the study night may increase patient anxiety and decrease sleep quality.

One problem with performing unattended studies in the home is that patients may be anxious about the portable monitor breaking down, or the electrodes falling off. During this study, all electrodes stayed in place. On one of the acclimatisation nights, all sleep study data was lost, and this was traced to the connecting cable becoming loose between the interface box and the main patient unit, when the patient retired to their bed. The acclimatisation night may help to reduce such anxieties. Night to night variability is also going to occur between lab and home study nights, in particular at the milder end of the disease spectrum (Wittig et al 1984), although this factor alone is going to affect both lab and home studies.

In conclusion, the preliminary findings presented here suggest that the MSLT and MWT can either be performed after a night's sleep at home or following standard MSLT guidelines (Carskadon et al 1986). A larger sample size is being obtained to confirm these observations and improve the low statistical power currently present in this study. Results suggest that neurophysiological measurements recorded at home demonstrate significantly better sleep quality than in the lab. It has been suggested that neurophysiological recording of sleep is of little diagnostic benefit in the majority of patients suspected of SAHS, where limited respiratory monitoring is sufficient (Douglas et al 1992). Perhaps it would be possible to routinely use activity monitoring (Aubert-Tulkens et al 1987) to cheaply and non-invasively record patient's sleep

duration at home the night before an MSLT/MWT. However, for SAHS patients with evidence of coexisting sleep disorders, and patients in research studies, such as that performed in Chapter 5, neurophysiological sleep monitoring is required (Douglas et al 1992). The question then arises as to whether this recording should take place in the lab, or in the home, and this may form the subject of future studies.

Chapter 9

Conclusions and Future Work

The correlational studies presented in this thesis found mainly weak or non-significant relationships between nocturnal SAHS variables and measures of daytime function. In the previous correlational studies discussed in Chapter 2, moderate or weak relationships were reported, in limited areas of daytime function. Results of previous studies are difficult to compare with the current study, due to differences in study size, design and outcomes assessed. Previous studies can be criticised for recruiting small numbers of patients (less than 30 in Roth et al 1980, Stepanski et al 1984, Findley et al 1986, Greenberg et al 1987, Bedard et al 1991b, Cheshire et al 1992, Borak et al 1996). Such sample sizes may fail to find positive relationships which do exist, or spuriously find relationships which do not. None of the previous large-number correlational studies included a wide range of nocturnal measures (Yesavage et al 1985, Millman et al 1989, Smith & Shneerson 1995) and/or daytime function measures (Yesavage et al 1985, Guilleminault et al 1988b, Roehrs et al 1989, Millman et al 1989, Poceta et al 1992, Smith & Shneerson 1995), thus making comparisons between studies difficult. Studies can also be criticised for using selected, severe SAHS patient samples (Roth et al 1980, Bedard et al 1991b) which are non-representative of the clinic population. In addition, only 3 previous studies controlled for age in their correlational analysis (Yesavage et al 1985, Cheshire et al 1992, Kim et al 1997). The current study improved on these previous studies by testing a wide ranging, large patient sample, in many areas of daytime function.

The data presented in this thesis demonstrates a lack of strong nocturnal predictors of daytime function in a group of unselected SAHS patients. However, some statistically significant associations are reported in this thesis, and although they are at most moderate in size, they are derived from a diverse patient sample, using a wide range of daytime and nocturnal measures, suggesting the associations have been intensively sought. The reality may be that the daytime outcome variables assessed in this thesis

are predicted by multiple nocturnal variables, each accounting for only small amounts of the variance. Alternatively, the current measures used to detect features of SAHS are not sophisticated enough to quantify factors affecting daytime function in a heterogeneous patient sample. Experimental sleep fragmentation studies in normal subjects have demonstrated that repetitive microarousals from sleep lead to decrements in daytime function of a similar nature to those found in sleep apnoeics (Philip et al 1994, Roehrs et al 1994, Martin et al 1996 & 1997b). CPAP therapy reduces respiratory events and microarousals from sleep, and treatment related improvements in many areas of daytime function have been identified following CPAP (Lamphere et al 1989, Sangal et al 1992b, Engleman et al 1994a, 1998). Such evidence strongly suggests that there is a causal relationship between nocturnal SAHS features and daytime function, but does not clarify which are the key nocturnal variables which determine daytime impairments.

A correlational study, by design, is highly susceptible to inter-individual residual variation. As discussed in Chapter 5, it is possible that unknown or unmeasurable factors are affecting daytime function in SAHS. Further work is required to identify these inter-individual patient differences. For example, measurement of a patient's motivation and competitiveness and their perception of their ability to upgrade themselves on the test day could be undertaken. Detailed descriptions of the patient's daily routine and their occupation in terms of activity levels and sleepiness thresholds can be measured. In addition, the duration since disease onset, and the patient's perception of their level of adaptation to their disease could be estimated. However, such behavioural questions as these are difficult to quantify.

The lack of significant correlations can alternatively be explained by the experimental measures used. Only conventional PSG variables were measured in this project, in an attempt to identify predictors of daytime dysfunction that could be implemented into standard lab procedures to determine who requires CPAP therapy. As no strong nocturnal predictors of daytime function were identified, perhaps more sophisticated measures and analytical techniques need to be implemented. Further analysis can be

performed on the nocturnal PSG data presented in Chapter 5, by identifying sleep stage specific events, interarousal durations and respiratory events with 30-50% reductions in thoracoabdominal movement, for example. Such variables could be subsequently correlated with daytime function measures. With the current EEG data, it would also be possible to perform spectral analysis of the EEG to identify subtle changes in EEG frequency (Rees et al 1995, Drinnan et al 1996). Future studies could also incorporate more sophisticated nocturnal SAHS measures in a large correlational study with a broad battery of daytime tests. Detectors of subtle autonomic arousals such as the Finapres device (Davies et al 1993b, Rees et al 1995) and measures of pulse transit time (Pitson et al 1994, Bennett et al 1998) could be included. Pleural pressure swings measured with oesophageal balloons (Milic-Emili et al 1964, Issa & Sullivan 1984), and flow limitation using nasal cannulae (Hosselet et al 1998) could also be measured. However, many of these sophisticated detection techniques are more invasive than standard recording methods, and may interfere with sleep.

As demonstrated in Chapter 8, results suggest that patients sleep better at home than in the lab. This could be due to less instrumentation used at home. Perhaps, home PSG monitoring rather than invasive techniques are required to identify predictors of daytime dysfunction. A future study could compare full portable PSG in the home and in the sleep lab in a crossover design to look solely at the effect of the unattended home environment versus the sleep lab.

The lack of correlations presented could also be due to the daytime measures used. The MSLT and MWT EEG data in this thesis could be analysed further in future work. The raw EEG data is available to assess more subtle measures of sleep onset latency. Brief periods of sleep (<15 seconds), so called 'microsleeps' (Harrison & Horne 1996a, Doghramji et al 1997), could be measured and correlated with nocturnal SAHS measures. In addition, spectral analysis of the EEG from daytime tests could be performed to identify subtle changes in EEG frequency (Rees et al 1995, Drinnan et al 1996). Such sensitive measures as these may identify EEG

changes in the patients who demonstrated ceiling effects on the MWT with the existing sleep latency criteria used in Chapter 5.

The strongest nocturnal versus daytime relationships in this thesis were found with self-reported questionnaires, incorporating trait assessments. In these questionnaires patients were asked to rate their well-being and symptoms from recent past events in their real-life. Improvements in ESS were significantly associated with CPAP use (Chapter 7), indicating that patients who felt an improvement in their sleepiness tend to be those who used therapy the most. In addition, Chapter 6 found the MWT was better related to other daytime function measures than the MSLT. Although the MWT is a state assessment, its instruction 'to try and stay awake' is more analogous to real-life, and is experienced by many patients every day. Future studies should record daytime function in these 'real-life' situations. For example, the portable PSG monitor described in Chapter 8 (Compumedics S, Australia) could be worn for 24 hours. The daytime EEG could be scored for microsleeps, and complemented with patient reports of lapses in concentration and attention across their daily routine. Wearing any visible equipment such as portable EEG is likely to cause embarrassment and thus increase alertness. Therefore a sufficient familiarisation session would also be required. It is likely that further technological developments will occur and in an ideal world, such lightweight ambulatory EEG monitoring will consist of small sensors on the scalp which transmit EEG data by telemetry.

Further understanding of cognitive decrements in SAHS can also be studied by newer technologies, such as computerised topographic brain mapping and cerebral blood flow imaging. Following on from the work of Martin et al (1996, 1997b), I am currently analysing data from a pilot study I performed examining the effect of sleep fragmentation on topographically mapped sensory evoked potentials in normal subjects. This study may identify areas of the brain where cognitive processing has been affected by sleep fragmentation. Such work could then lead to large scale studies on sleep apnoeics, possibly to identify why some patients with similar disease severity suffer cognitive decrements and others not, as demonstrated by the lack of strong

correlations in Chapter 5. Previous small sample studies on topographic mapping in sleep apnoeics (Walsleben et al 1993, Sangal & Sangal 1995) have found conflicting results, with Walsleben et al (1993) reporting delayed auditory P300 latencies in the right parietal area, whereas Sangal & Sangal (1995) reported delayed visual P300 latencies in all brain areas except the right parietal region, thus further large scale studies are required. Recent preliminary work in monitoring cerebral blood flow using single photon emission computed tomography (SPECT) has identified deficits in blood flow to a variety of brain areas, including the inferior frontal lobe, the temporal lobe, and in 4 cases blood flow deficits were identified across the whole cortex and cerebellum (Tainturier et al 1998). Again this technique requires large sample studies in the future. Technological advances such as virtual reality will allow the development of more sophisticated driving simulators for future assessments of cognitive performance and daytime sleepiness. Ideally an EEG topographically mapped brain could be monitored during very realistic driving simulations, and then analysed by spectral EEG analysis.

In conclusion, future studies need to use such new technologies to take the sleep experiments into the patient's real-life environment, including the workplace and the vehicle, two areas where patients complain of decreased functioning. Determining the causes of poor functioning in these areas are of great public health interest.

Meanwhile, the results suggest that the measurement of apnoea/hypopnoea frequency and arousal frequency during clinical studies of breathing during sleep is less strongly predictive of daytime function decrements than had previously been thought, and that alternative, more strongly predictive, measures must be actively sought.

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APPENDIX A

Below is the in-house Symptom Questionnaire

Name:

Study:

Date:

Treatment:

Have you suffered from any of the following problems in the recent past? Please circle the appropriate value to show how frequently, if at all, these symptoms have been occurring.

Heavy snoring

NEVER	LESS THAN ONE NIGHT PER MONTH	BETWEEN ONE NIGHT PER MONTH AND ONE NIGHT PER WEEK	ONE TO THREE NIGHTS PER WEEK	THREE TO SIX NIGHTS PER WEEK	EVERY NIGHT
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Choking during the night

NEVER	LESS THAN ONE NIGHT PER MONTH	BETWEEN ONE NIGHT PER MONTH AND ONE NIGHT PER WEEK	ONE TO THREE NIGHTS PER WEEK	THREE TO SIX NIGHTS PER WEEK	EVERY NIGHT
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Breathing pauses witnessed by partner

NEVER	LESS THAN ONE NIGHT PER MONTH	BETWEEN ONE NIGHT PER MONTH AND ONE NIGHT PER WEEK	ONE TO THREE NIGHTS PER WEEK	THREE TO SIX NIGHTS PER WEEK	EVERY NIGHT
-------	-------------------------------------	---	---------------------------------------	------------------------------------	----------------

Difficulty in staying asleep at night

NEVER	LESS THAN ONE NIGHT PER MONTH	BETWEEN ONE NIGHT PER MONTH AND ONE NIGHT PER WEEK	ONE TO THREE NIGHTS PER WEEK	THREE TO SIX NIGHTS PER WEEK	EVERY NIGHT
-------	-------------------------------------	---	---------------------------------------	------------------------------------	----------------

Unrefreshed / unsatisfied by sleep on awakening in the morning

NEVER	LESS THAN ONE NIGHT PER MONTH	BETWEEN ONE NIGHT PER MONTH AND ONE NIGHT PER WEEK	ONE TO THREE NIGHTS PER WEEK	THREE TO SIX NIGHTS PER WEEK	EVERY NIGHT
-------	-------------------------------------	---	---------------------------------------	------------------------------------	----------------

Napping during the daytime (9am-5pm)

NEVER	LESS THAN ONE NIGHT PER MONTH	BETWEEN ONE NIGHT PER MONTH AND ONE NIGHT PER WEEK	ONE TO THREE NIGHTS PER WEEK	THREE TO SIX NIGHTS PER WEEK	EVERY NIGHT
-------	-------------------------------------	---	---------------------------------------	------------------------------------	----------------

Napping in the evenings (after 5pm)

NEVER	LESS THAN ONE NIGHT PER MONTH	BETWEEN ONE NIGHT PER MONTH AND ONE NIGHT PER WEEK	ONE TO THREE NIGHTS PER WEEK	THREE TO SIX NIGHTS PER WEEK	EVERY NIGHT
-------	-------------------------------------	---	---------------------------------------	------------------------------------	----------------

Do you drive (please circle answer) YES NO

If so, how many miles per year? _____miles

Please circle answers to reflect your recent experience of driving

Feeling sleepy whilst driving

NEVER	LESS THAN ONE NIGHT PER MONTH	BETWEEN ONE NIGHT PER MONTH AND ONE NIGHT PER WEEK	ONE TO THREE NIGHTS PER WEEK	THREE TO SIX NIGHTS PER WEEK	EVERY NIGHT
-------	-------------------------------------	---	---------------------------------------	------------------------------------	----------------

Falling asleep whilst driving

NEVER	LESS THAN ONE NIGHT PER MONTH	BETWEEN ONE NIGHT PER MONTH AND ONE NIGHT PER WEEK	ONE TO THREE NIGHTS PER WEEK	THREE TO SIX NIGHTS PER WEEK	EVERY NIGHT
-------	-------------------------------------	---	---------------------------------------	------------------------------------	----------------

APPENDIX B

Below is the in-house sleep/wake questionnaire given to all individuals referred to the sleep centre with a suspected sleep disorder.

NAME :

DATE

SLEEP/WAKE QUESTIONNAIRE

Please find enclosed two questionnaires, one for you (marked patient) and a shorter one (marked partner) for your partner if you have one. The aim of these simple questionnaires is to discover the extent of your problem. It would be very helpful if you could arrange to fill them in and hand them to the doctor seeing you in the hospital clinic or to the Sleep Centre, Ward 48, Royal Infirmary of Edinburgh, at your next visit.

The questionnaire for your partner must be filled in independently by him/her without consulting you. You may get help, however, from your partner in answering Questions 9, 11 and 20.

For most questions several options are available, underline the answer which is most appropriate.

The answers will form part of your medical records and remain confidential.

Thank you for your co-operation.

PERSONAL INFORMATION: DATE:

Name: Age: Date of Birth :

Address : Tel No:

..... Height: Weight:

..... Collar Size : Marital Status:

Children:	Number :	Age	Sex

Occupation: current for years
 previous for years
 for years
 for years

Are you a : smoker / non-smoker / ex-smoker (for years)

What did / do you smoke:	cigarettes	yes/no	Number per day
	cigars	yes/no	Number per day
	tobacco (own rolled)	yes/no	Oz. per week
	tobacco (pipe)	yes/no	Oz. per week

Do you drink:	tea	yes/no	cups per day
	coffee	yes/no	cups per day
	wine	yes/no	glasses per day
	beer	yes/no	pints per week
	spirits	yes/no	drinks per week
	sherry/port	yes/no	glasses per week.....

Any alcohol immediately before going to bed: yes/no

What medication, including sleeping pills are you taking at present?

Name	Dose	How long have you been taking it?
1.
2.
3.
4.
5.
6.
7.
8.

PAST MEDICAL HISTORY

If you have had the following illnesses, please give details:

Illness		
Asthma	yes/no
Bronchitis	yes/no
Emphysema	yes/no
Diabetes	yes/no
Heart attacks	yes/no
High blood pressure	yes/no
Ankle swelling	yes/no
Tonsillitis	yes/no
Hay fever	yes/no
Broken nose	yes/no
Bed wetting	yes/no
Nose operations	yes/no
Throat operations	yes/no
Nerve problems	yes/no

- 1. When do you go to bed at night on average?
- 2. When do you finally wake up in the morning on average?
- 3. How long do you take to fall asleep at night?
- 4. How often do you wake between going to bed and getting up in the morning?
never / 1-3 times / 3-6 times / more than 6 times per night
- 5. Do you do shift work? If so, please specify shifts and how long you are on each shift
.....
- 6. How many times have you wet the bed in the last year?
never / occasionally / 2-6 times / more than 6 times
- 7. How often have you woken with a headache each week?
never / 1-2 times / 2-5 times / more than 5 times
- 8. How likely are you to doze off or fall asleep, in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

- 0 = would **never** doze
- 1 = **slight** chance of dozing
- 2 = **moderate** chance of dozing
- 3 = **high** chance of dozing

<u>Situation</u>	<u>Chance of Dozing</u>
Sitting and reading
Watching TV
Sitting, inactive in a public place (e.g. a theatre or a meeting)
As a passenger in a car for an hour without a break
Lying down to rest in the afternoon when circumstances permit
Sitting and talking to someone
Sitting quietly after a lunch without alcohol
In a car, while stopped for a few minutes in traffic
TOTAL	=====

9. Do you snore during sleep?
Yes/No
If yes:
 - a) How long have you snored loudly?
Always since childhood / last 5 years / 3 years / 1 year
 - b) Do you snore every night / most nights/ occasional nights
 - c) Do you snore on your back only / on back and side / in all positions
10. Do you have a regular bed-partner or room-mate?
yes / no / previously but not currently
11. Has your bed-partner/room-mate ever noticed that you stop breathing when asleep?
yes / no
12. Do you need to go to the toilet at night?
never / occasionally / 1-2 times / more than 2 times per night
13. Do your ankles swell? If so, for how long
yes / no months / years
14. Have you ever had hallucinations when you have been falling off to sleep or waking up?
yes / no
15. Have you ever had episodes when you body or part of your body has become floppy in response to an emotional stimulus?
yes / no
16. Have you ever had episodes when you have woken up and been unable to move?
yes / no
If so, how often?
once / less than 5 times / more than 5 times
17. In the morning do you feel that your nights sleep was refreshing/satisfactory?
always / 4-6 nights per week / 1-3 nights per week / never
18. Have you or your partner noticed any change in your sex drive ?
increased / unchanged / decreased / non-existent
19. How many times have you woken choking or suffocating in the past month?
never / 1-2 times / 3-6 times / more than 6 times
20. How often is your bed-partner or room-mate, disturbed each week because of excessive arm and/or leg movements?
never / 1-5 times / 5-10 times / more than 10 times / no bed partner

21. Are you ever forced to have a nap during the day?
yes / no
If so, how many naps (5 minutes) do you have per day?
1-2 / 2-4 / 4-6 / more than 6
22. How many times have you fallen asleep against your will (for example, while eating, driving or in company) in the last year?
never / 1-2 / 2-4 / more than 4 (give details below)
23. For how long have you been sleepy during the day?
3 months / 3-6 months / 6-12 months / over 12 months / over 10 years
24. Do you drive?
yes / no
25. Have you ever had, or nearly had an accident because of falling asleep while driving?
yes / no (give details below)
26. Have you, your partner or family noticed any change in your personality?
yes / no
If so, specify :
.....
.....
27. Has you weight changed in recent years?
yes / no down / up
If so, what is the change stones lbs
When did your weight change occur :
28. Have you any comments on the questions above?
.....
.....
.....
.....
.....
Additional comments:
.....
.....
.....
.....
.....

NAME :

DATE :

SLEEP WAKE QUESTIONNAIRE - PARTNER

PERSONAL INFORMATION: DATE:

NAME: PATIENT'S NAME

AGE: DATE OF BIRTH:

1. Does your partner drink?

tea	yes/no	cups per day
coffee	yes/no	cups per day
wine	yes/no	glasses per day
beer	yes/no	pints per week
spirits	yes/no	drinks per week
sherry/port	yes/no	glasses per week

Any alcohol immediately before going to bed: yes/no

2. How likely does your partner doze off or fall asleep, in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0	=	would never doze
1	=	slight chance of dozing
2	=	moderate chance of dozing
3	=	high chance of dozing

Situation	Chance of Dozing
Sitting and reading
Watching TV
Sitting, inactive in a public place (e.g. a theatre or a meeting)
As a passenger in a car for an hour without a break
Lying down to rest in the afternoon when circumstances permit
Sitting and talking to someone
Sitting quietly after a lunch without alcohol
In a car, while stopped for a few minutes in traffic
TOTAL	=====

- 3. Is your partner forced to have a nap during the day?
yes / no
If so, how many naps (5 minutes) does he/she have per day?
1-2 / 2-4 / 4-6 / more than 6
- 4. How many times has your partner fallen asleep against his/her will (for example, while eating, driving or in company) in the last year?
never / 1-2 / 2-4 / more than 4 (give details below)
- 5. For how long has your partner been sleepy during the day?
3 months / 3-6 months / 6-12 months / over 12 months / over 10 years
- 6. Does your partner drive?
yes / no
- 7. Has your partner ever had, or nearly had an accident because of falling asleep while driving?
yes / no (give details below)
- 8. Has your partner or family noticed any change in his/her personality?
yes / no

If so, specify:

.....

.....

.....

.....

APPENDIX C

Below is the sleep diary given to patients in the home versus lab study (Chapter 8)

Sleep Diary

Night: at home / in sleep lab (please delete as appropriate)

Name:

Date of Birth:

Date of study:

1. What time did you go to bed?
2. What time do you think you fell asleep?
3. How many times were you aware of waking up during the night?
4. What time do you think you woke up in the morning?
5. What time did you get out of bed in the morning?
6. Was last night's sleep representative of a normal night's sleep for you?

yes..... No..... (please tick yes or no)

Comments.....

7. How refreshed did you feel on awakening? (ring appropriate number)

1	2	3	4	5
unrefreshed				refreshed

8. Please write down any further comments about last nights sleep

.....

.....

.....

Thank you for your co-operation

APPENDIX D

Articles, abstracts and presentations resulting from this thesis.

Original Articles

Kingshott RN, Sime PJ, Engleman HM, Douglas NJ. Self assessment of daytime sleepiness: patient versus partner. *Thorax* 1995; 50:994-995.

Kingshott RN, Engleman HM, Deary IJ, Douglas NJ. Does arousal frequency predict daytime function? *Eur Respir J* (In press).

Abstracts and Presentations

Assessment of daytime sleepiness in new sleep clinic patients and their partners using the Epworth Sleepiness Scale (ESS). Kingshott RN, Sime PJ, Engleman HM, Douglas NJ. Proceedings of the British Sleep Society. London; September 1995.

Factors affecting daytime function in sleep apnea. Kingshott RN, Douglas NJ. *Am J Respir Crit Care Med* 1997; 155:A847.

A comparison of the MSLT and the MWT in SAHS patients. Kingshott RN, Douglas NJ. Proceedings of the 5th international sleep and breathing symposium. Edinburgh, October 1997.

Relationships between the MSLT and MWT and other measures of daytime function in SAHS patients. Kingshott RN, Douglas NJ. *Am J Respir Crit Care Med* 1998; 157:A51.

Self assessment of daytime sleepiness: patient versus partner

Ruth N Kingshott, Patricia J Sime, Heather M Engleman, Neil J Douglas

Abstract

Background - Patients with the sleep apnoea/hypopnoea syndrome (SAHS) and their spouses often differ in their assessment of the patient's sleepiness. A study was therefore undertaken to investigate whether either the patient's or partner's rating on the Epworth sleepiness scale (ESS) was better related to illness severity.

Methods - Nocturnal variables (apnoeas - hypopnoeas/hour (AHI) and arousals/hour) and patient and partner ESS scores were compared in 103 new patients attending the sleep clinic.

Results - Mean patient and partner ESS scores were not different. In the whole population neither patient nor partner ESS variables correlated with AHI or arousal frequency. In the patients with SAHS (AHI ≥ 15), partner ESS correlated weakly with AHI, but patient ESS did not.

Conclusions - This study suggests that neither patient nor partner ESS ratings are strong predictors of SAHS severity.

(Thorax 1995;50:994-995)

Keywords: sleep apnoea/hypopnoea syndrome, sleepiness, partner.

Excessive sleepiness is the most prevalent daytime symptom of the sleep apnoea/hypopnoea syndrome (SAHS),¹ resulting in an increased risk of vehicle accidents.² The multiple sleep latency test (MSLT)³ and its variant, the maintenance of wakefulness test (MWT),⁴ are used as objective methods for measuring daytime sleepiness, but are labour intensive and expensive to conduct. More simply, the Epworth sleepiness scale (ESS),⁵ a self administered questionnaire, provides a subjective estimation of daytime sleepiness. There is frequently a discrepancy between the patient and their partner's ESS assessment. The aim of this study was to determine if patient or partner's assessment of sleepiness is a better predictor of SAHS severity.⁶

Methods

SUBJECTS

One hundred and three patients referred for assessment of suspected SAHS were studied. Patients subsequently diagnosed with narcolepsy, periodic limb movement disorder, psychological or psychiatric illness were excluded from the study. The patients consisted of 87 men and 16 women of mean (SD) age 48 (13)

years, with a mean apnoea/hypopnoea index (AHI) of 28 (22)/hour slept, and a mean arousal index (see below) of 25 (18)/hour slept.

Overnight clinical polysomnography⁷ was recorded in the Scottish National Sleep Laboratory, with the nocturnal variables defined as follows: (1) An apnoea is the cessation of airflow for at least 10 seconds,⁸ and a hypopnoea is a 50% reduction in thoracoabdominal movement for at least 10 seconds.⁸ (2) An arousal is an increase in electromyographic tone for at least 1.5 seconds associated with the return of alpha or theta rhythm.⁹

Patients' sleepiness was independently rated by both patients and partners using the ESS, which yields a total score corresponding to the chance of dozing in each of eight real life situations.⁵ In addition, the minimum ESS (minESS) and the maximum ESS (maxESS) values for each couple were analysed.

DATA ANALYSIS

Data were analysed using the SPSS-PC - (SPSS Inc, Chicago, USA). Patient and partner ESS scores were compared using two tailed Wilcoxon tests, and relationships between nocturnal variables and ESS variables were evaluated by Spearman rank correlations.

Results

Patient and partner mean ESS scores (table 1) were not significantly different. In the whole population (table 2) no significant correlations were seen between nocturnal variables and ESS scores (figure). In the SAHS diagnosed subgroup (AHI ≥ 15), patient ESS did not correlate significantly with nocturnal variables, whilst partner ESS and minESS scores correlated weakly but significantly with AHI (table 2). One quarter of patients with severe SAHS (AHI ≥ 50 , n = 16) scored below 10 on the ESS, in contrast to a previous study¹ where all patients with severe SAHS (n = 19) scored 10 or more.

Table 1 Comparisons of mean (SD) patient and partner ESS scores in the whole population and in those with AHI ≥ 15

	Patient mean ESS score	Partner mean ESS score	p value
Whole sample (n = 103)	12 (5)	12 (4)	NS
AHI ≥ 15 (n = 66)	12 (5)	11 (4)	NS

ESS = Epworth sleepiness scale; AHI = apnoea - hypopnoea index (per hour slept); NS = non-significant (p > 0.05).

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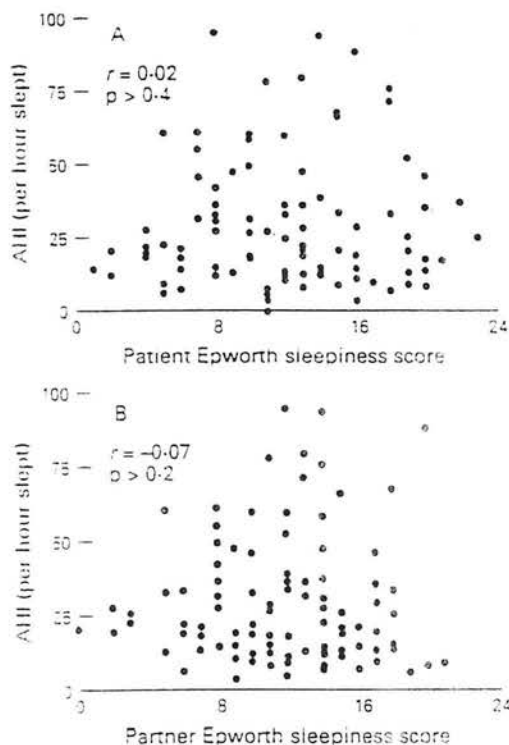
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Table 2 Correlation matrix of nocturnal variables with ESS variables

	Patient ESS score	Partner ESS score	MaxESS score	MinESS score
Whole sample (n = 103)				
AHI	0.02	-0.07	-0.13	0.10
Arousal index	0.01	-0.05	-0.06	0.03
AHI ≥ 15 (n = 66)				
AHI	0.14	0.27**	0.11	0.32***
Arousal index	-0.001	0.07	0.04	0.04

ESS = Epworth sleepiness scale; AHI = apnoea-hypopnoea index (per hour sleep); 95% CI = 95% confidence intervals for significant r values. ** $p < 0.01$.



Rank correlation of apnoea-hypopnoea index (AHI) and Epworth sleepiness scale score in (A) patient and (B) partner.

Discussion

Analyses of the whole population indicate that patient and partner ESS scores are similar, in keeping with a smaller recent study.¹⁰ However, we have extended that study by showing that, in the whole group, there were no significant correlations between ESS variables and nocturnal variables for ratings of sleepiness by either the patient or partner.

In the subgroup of SAHS diagnosed patients (AHI ≥ 15) the patient's ESS rating was not significantly related to AHI. This contrasts with an earlier study¹¹ where correlations ($r = 0.44$, $p < 0.001$) were found between patient ESS score and AHI in patients with SAHS by the originator of the ESS. We can see no obvious explanations for the discrepancy. The partner's ESS rating was significantly correlated with AHI, but only weakly. The minimum ESS score in a couple was better correlated with AHI than the larger of the two scores.

We believe that our failure to find significant correlations between ESS and SAHS severity

has several causes which reflect the problems with subjective ratings. As part of human nature, some patients maximise and others minimise their symptoms. In addition, some patients with severe SAHS and severe objective sleepiness are so obtunded that they do not appreciate the severity of their symptoms, at least until after they are treated.¹² Our failure to find any better correlation using partners' estimates of ESS may be due to a combination of two factors: (1) partners only observe patients over a limited part of the day, and thus have difficulty in making an accurate estimate on all points of the scale, and (2) the patients' complaints about sleepiness may influence the scoring by their spouses.

Alternatively, the lack of correlation between ESS and polysomnography results could mean that polysomnography is not providing useful measurements of disease severity. This seems unlikely as daytime sleepiness measured by the MSLT³ correlates significantly with apnoea-hypopnoea frequency and micro-arousal frequency but not with ESS score.¹³ Our data are supported by studies using other subjective sleepiness assessments - for example, Dement *et al.*¹⁴ using the Stanford sleepiness scale found that subjective sleepiness correlated with sleep latency in normal subjects but not in patients with sleep apnoea.¹⁴

We conclude that the clinical predictive value of ESS scores is limited, with the results indicating that neither the patients' scores nor those of their partners are strong predictors of disease severity. Hence, the ESS alone cannot be used to determine the mode of investigation or the likelihood of an individual having SAHS.

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